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The Reporting Quality, Scientific Rigor, and Ethics of Randomized Placebo-Controlled Trials of Traditional Chinese Medicine Compound Formulations and the Differences Between Chinese and Non-Chinese Trials

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ABSTRACT

BACKGROUND: An increasing number of randomized placebo-controlled trials involving traditional Chinese medicine (TCM) compound formulations have been implemented worldwide.

OBJECTIVE: The aim of this study was to assess the reporting quality, scientific rigor, and ethics of randomized placebo-controlled trials of TCM compound formulations and compare these differences between Chinese and non-Chinese trials.

METHODS: English-language databases included the following: PubMed, OVID, EMBASE, and Science Citation Index Expanded. Chinese-language databases included the following: Chinese Biomedical Literature Database, Wanfang Database, Chinese Scientific and Technological Periodical Database, and the China National Knowledge Infrastructure. All were searched from respective inception to March 2009 to identify randomized placebo-controlled trials involving TCM compound prescriptions. Two reviewers independently assessed the retrieved trials via a modified Consolidated Standard of Reporting Trials (CONSORT) checklist and some evaluation indices that embodied the TCM characteristics or the scientific rigor and ethics of placebo-controlled trials. Trial publishing time was divided into 3 intervals: phase 1 (≤1999); phase 2 (2000–2004); and phase 3 (2005–2009). The number and percentage of trials reporting each item and the corresponding differences between Chinese (mainland China, Hong Kong, and Taiwan) and non-Chinese (eg, Japan, United States, Australia, Korea, and United Kingdom) trials were calculated. Moreover, the influence of trial publishing time on the reporting of CONSORT items and the differences in the number of items reported for each time interval between Chinese and non-Chinese trials were assessed.

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RESULTS: A total of 324 trials from China and 51 trials from other countries were included. A mean of 39.7% of the CONSORT items across all Chinese trials and 50.2% of the items across all non-Chinese trials were reported. The number of the reported CONSORT items all increased over time in both groups and the gap between Chinese articles and non-Chinese articles gradually decreased. Additionally, of the 324 Chinese articles, 137 (42.28%) reported TCM syndrome type, 113 (34.88%) reported the diagnostic criteria of diseases for TCM, and 69 (21.30%) reported efficacy evaluation indices of TCM. Of the non-Chinese articles, 3 (5.88%) reported TCM syndrome type and 1 (1.96%) reported the diagnostic criteria of diseases and evaluation indices of efficacy for TCM. It was found that 45.37% and 6.17% of Chinese articles reported the standard intervention for the diseases being treated and the emergency plan, respectively, compared with 23.53% and 9.80% for the non-Chinese articles; 33.02% and 10.49% of Chinese articles reported informed consent and ethics committee approval, respectively, compared with 92.16% and 82.35% for the non-Chinese articles. With regard to placebo ethics, 38.89% of the Chinese trials and 23.53% of the non-Chinese trials found it would not be ethically acceptable to use placebo alone in the control group.

CONCLUSIONS: The data indicate that the reporting quality of the included trials on TCM compounds has improved over time, but still remains poor regardless of Chinese or non-Chinese trials. Across all trials, particularly Chinese trials, the reporting of the CONSORT items was inadequate (39.7%). The difference in the mean number of the reported CONSORT items between Chinese trials and non-Chinese trials narrowed from phase 1 (10.0 vs 13.8) to phase 3 (14.4 vs 17.4). Moreover, a large number of trials, especially non-Chinese trials (94.1%), were lacking syndrome differentiation of TCM. More importantly, in many placebo-controlled trials, especially Chinese trials, the use of placebo was not justified and was ethically contradictory. (*Curr Ther Res Clin Exp.* 2010;71:30–49)

KEY WORDS: reporting quality, scientific rigor, ethics, traditional Chinese medicine compound formulation, placebo, randomized controlled trial, CONSORT statement.

INTRODUCTION

With the advancement of science, medical technology has witnessed rapid improvement.[1] However, for certain diseases, there is still a lack of effective treatment methods. Therefore, both doctors and patients may turn to complementary and alternative medicine (CAM)[2] such as traditional Chinese medicine (TCM).[3–6] TCM is a medical system in China that has been used for thousands of years to diagnose and treat diseases.[3] The recognition and treatment of diseases in TCM are different from those in Western medicine. TCM theories are based on syndrome differentiation and holistic medicine. It includes treatments such as Chinese herbal medicine, acupuncture, and Qigong.[7] A formulation that contains ≥2 Chinese herbs[8] better conforms to TCM theories and better reflects the characteristics of TCM than the administration of a single herb. Generally, a compound formulation is prescribed according to the principle

"Monarch, Minister, Assistant and Guide." The Monarch acts as the chief drug for treating the disease and is composed of one or more herbs; the Minister serves to intensify the effect of the Monarch drug; the Assistant helps to deals with the secondary symptoms or inhibits the toxicity of the Monarch drug; and the Guide drug leads the other herbs to the diseased parts and balances the effects of all herbs. TCM compound formulations have been widely used to treat disease in China. In recent decades, the use of TCM has become more popular, sometimes as a complementary treatment to Western medicine, throughout the world.[9,10] TCM has been adopted in modified forms in other countries, such as Korea, Japan, United States, and Australia.[11]

In the past 2 decades, randomized, double-blind, placebo-controlled, clinical trials have been considered the general standard in clinical research of therapeutic interventions.[12] An increasing number of randomized placebo-controlled trials of TCM compound formulations have been designed and implemented.[13] However, the reporting quality of these trials or whether placebo-controlled trials meet the requirements of scientific rigor and ethics is unclear.

Some research has revealed that the reporting quality of TCM trials was poor. Gagnier et al[14] found that randomized controlled trials (RCTs) of herbal medicine interventions reported less than half of the necessary information of the modified Consolidated Standard of Reporting Trials (CONSORT) items. Wang et al[15] assessed the reporting quality of RCTs of TCM interventions in 13 randomly selected journals from mainland China, which indicated that only 39.4% of the modified CONSORT items were reported across all included trials. However, a search of the literature revealed that there had been no articles that assessed the reporting quality, scientific rigor, and ethics of randomized placebo-controlled trials of TCM compound prescription interventions.

The CONSORT statement was first published in 1996 and revised in 2001.[16,17] It was gradually introduced into China after 2001.[18] It has been endorsed by many leading medical journals and has been widely accepted as an international standard to improve the reporting quality of RCTs.[19] It includes a 22-item checklist and a flow diagram to guide researchers and writers on how to design and report clinical trials.[16] *Adequate reporting* is defined as reporting all items recommended by the CONSORT guidelines. Previous research indicates that the use of the CONSORT statement might help to improve the quality of reports of RCTs.[20] It is, however, not enough to assess the reporting quality of RCTs of TCM through the information suggested in CONSORT. In order to improve the reporting quality of RCTs of TCM, the Chinese Cochrane Center was authorized to establish CONSORT for TCM. In 2006, the draft version was completed.[21] However, some items still need further improvement. Therefore, after consultation with some experts of Chinese Evidence-Based Medicine/Cochrane Center, our research team jointly established a modified CONSORT checklist, some specific indices that reflect the characteristics of TCM, and other indices that should be reported in placebo-controlled trials, which were based on the CONSORT for TCM. This was done to be able to assess the reporting quality of randomized placebo-controlled trials of TCM compound formulation interventions.

The objective of the present study was to assess the reporting quality, scientific rigor, and ethics of randomized placebo-controlled trials of TCM compound formulation interventions. A secondary objective was to compare the corresponding differences between Chinese and non-Chinese trials.

METHODS

Literature Search Strategy

A literature search was conducted of 8 electronic databases including 4 English-language databases and 4 Chinese-language databases, from respective inception to March 2009. English language databases included the following: PubMed, OVID, EMBASE, and Science Citation Index Expanded. Chinese language databases included the following: Chinese Biomedical Literature Database, Wanfang Database, Chinese Scientific and Technological Periodical Database, and the China National Knowledge Infrastructure. The search terms used in PubMed were as follows: (*"Placebos"{Mesh}* OR *placebo** OR *sham*) AND (*"Medicine, Chinese Traditional"{Mesh}* OR *herb**). The search terms were similar for all databases. The publication type of articles was limited to RCTs, and the language of articles was limited to English and Chinese.

Study Selection

Articles that satisfied the criteria of randomized placebo-controlled clinical trials of TCM compound prescription interventions were identified. Exclusion criteria were as follows: experimental studies; nonclinical research (eg, methodologic studies, systematic reviews, meta-analyses, and other review literature); and duplicate studies. In addition, some articles involving CAM other than TCM compound formulations, herb medicine monomer, or single herb as the intervention group were excluded. Two authors (X.-M.L. and J.-J.F.) independently screened the title and abstract of each article to determine its eligibility for inclusion. When trial inclusion could not be determined by titles and abstracts, full texts were retrieved. Disagreements were resolved by consensus.

Assessment Contents

The CONSORT checklist was reviewed and 33 subitems extracted from the original 22-item CONSORT statement[22] formed a modified CONSORT checklist (**Table I**). Each subitem referred to an individual concept.

In addition, we summarized some TCM characteristic indices based on the statement of CONSORT for TCM as well as other indices that should be reported in placebo-controlled trials. Indices, which reflected the TCM characteristics, included the composition of each TCM compound, actions and indications of each TCM compound, and modern pharmacologic evidence of each active ingredient, TCM syndrome type, TCM diagnostic criteria for each disease, evaluation indices of efficacy for TCM, and interpretation of the results with TCM theories.[21] Some indices that should be reported in placebo-controlled trials included the manufacturing process of the placebo, the difference in sensory characteristics between the study preparation and the placebo, quality control surveillance of interventions, and number and name of trial registration (**Table II**). The use of placebo, which should smell, appear, and

Table I. The modified Consolidated Standard of Reporting Trials (CONSORT) checklist for reporting randomized placebo controlled trials of traditional Chinese medicine compound formulations.

Study Section	Standard CONSORT Items	Item No.	Subitem Description of CONSORT Checklist	Chinese Trials,* No. (%) (n = 324)	Non-Chinese Trials,† No. (%) (n = 51)	Statistic Value	*P*
Title and abstract	Title and abstract	1	How participants were allocated to interventions	302 (93.21)	45 (88.24)	0.940†	0.332
Introduction	Background	2	Scientific background and explanation of rationale	267 (82.41)	51 (100)	10.580§	0.001
Methods	Participants	3	Inclusion criteria for participants	291 (89.81)	51 (100)	4.497†	0.034
		4	Exclusion criteria for participants	204 (62.96)	40 (78.43)	4.638§	0.031
		5	The settings and locations where the data were collected	217 (66.98)	33 (64.71)	0.102§	0.749
	Interventions	6	Precise details of the interventions intended for each group	150 (46.30)	34 (66.67)	7.316§	0.007
	Objectives	7	Specific objectives and hypotheses	316 (97.53)	50 (98.04)	0.000†	1.000
	Outcomes	8	Clearly defined primary outcome measures	55 (16.98)	22 (43.14)	18.483§	<0.001
		9	Clearly defined secondary outcome measures	27 (8.33)	17 (33.33)	26.592§	<0.001
		10	Any methods used to enhance the quality of measurements	37 (11.42)	3 (5.88)	1.418§	0.234
	Sample size	11	How sample size was determined	18 (5.56)	18 (35.29)	41.543†	<0.001

(continued)

Table I (continued).

Study Section	Standard CONSORT Items	Item No.	Subitem Description of CONSORT Checklist	Chinese Trials,* No. (%) (n = 324)	Non-Chinese Trials,† No. (%) (n = 51)	Statistic Value	*P*
	Randomization sequence generation	12	Method used to generate the random allocation sequence	104 (32.10)	20 (39.22)	1.008§	0.315
		13	Details of any restriction of randomization	39 (12.04)	13 (25.49)	6.677§	0.010
	Allocation concealment	14	Allocation concealment	23 (7.10)	9 (17.65)	5.003†	0.025
	Randomization implementation	15	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups	18 (5.56)	7 (13.73)	3.505†	0.061
	Blinding	16	Whether or not participants were blinded to group assignment	205 (63.27)	49 (96.08)	21.700§	<0.001
		17	If done, how the success of blinding was evaluated	5 (1.54)	4 (7.84)	5.019†	0.025
	Statistical methods	18	Statistical methods used to compare groups for primary outcome(s)	254 (78.40)	48 (94.12)	6.948§	0.008
		19	Methods for additional analyses, such as subgroup and adjusted analyses	6 (1.85)	2 (3.92)	0.185†	0.668

(continued)

Table I (continued).

Study Section	Standard CONSORT Items	Item No.	Subitem Description of CONSORT Checklist	Chinese Trials,* No. (%) (n = 324)	Non-Chinese Trials,† No. (%) (n = 51)	Statistic Value	*P*
Results	Participant flow	20	Flow of participants through each stage	13 (4.01)	18 (35.29)	52.810‡	<0.001
		21	Describe protocol deviations from study as planned, together with reasons	12 (3.70)	7 (13.73)	7.235‡	0.007
	Recruitment	22	Dates defining the periods of recruitment	216 (66.67)	15 (29.41)	25.855§	<0.001
		23	Dates defining the periods of follow-up	54 (16.67)	23 (45.10)	21.829§	<0.001
	Baseline data	24	Baseline demographic and clinical characteristics of each group	257 (79.32)	40 (78.43)	0.021§	0.884
	Numbers analyzed	25	Intention-to-treat analysis	25 (7.71)	12 (23.53)	12.390§	<0.001
	Outcomes and estimation	26	For each primary and secondary outcome, a summary of results for each group	320 (98.77)	51 (100)	_	1.000‖
		27	For each primary and secondary outcome, the estimated effect size	83 (25.62)	6 (11.76)	4.671§	0.031
		28	The estimated effect precision (eg, 95% CI)	13 (4.01)	8 (15.69)	9.258‡	0.002

(continued)

Table I (continued).

Study Section	Standard CONSORT Items	Item No.	Subitem Description of CONSORT Checklist	Chinese Trials,* No. (%) (n = 324)	Non-Chinese Trials,† No. (%) (n = 51)	Statistic Value	*P*
	Ancillary analyses	29	Ancillary analyses	4 (1.23)	2 (3.92)	_	0.190‖
	Adverse events	30	Adverse events in each intervention group	154 (47.53)	35 (68.63)	7.845§	0.005
Discussion	Interpretation	31	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision	82 (25.31)	26 (50.98)	14.162§	<0.001
	Generalizability	32	Generalizability of the trial findings	244 (75.31)	31 (60.78)	4.753§	0.029
	Overall evidence	33	General interpretation of the results in the context of current evidence	85 (26.23)	24 (47.06)	9.268§	0.002

*Trials conducted in mainland China, Hong Kong, and Taiwan.

† Trials conducted outside of mainland China (eg, Japan, United States, Australia, Korea, and United Kingdom).

‡ Continuity correction χ^2 test.

§ Pearson χ^2 test.

‖ Fisher exact test.

Table II. Comparison of the number of Consolidated Standard of Reporting Trials (CONSORT) items reported for each time interval between Chinese and non-Chinese trials in randomized placebo-controlled trials of traditional Chinese medicine compound formulations.

	Chinese Trials* (n = 324)		Non-Chinese Trials† (n = 51)			
Trial Publishing Time	No. of Trials	CONSORT Items Reported, Mean (SD), No.	No. of Trials	CONSORT Items Reported, Mean (SD) No.	Statistic Value	*P*
Phase 1 (≤1999)	40	10.0 (3.0)	12	13.8 (4.3)	3.487‡	0.001
Phase 2 (2000–2004)	73	11.1 (2.6)	23	17.4 (3.8)	–5.945§	<0.001
Phase 3 (2005–2009)	211	14.4 (3.8)	16	17.4 (4.5)	–2.526§	0.012
From inception to March 2009	324	13.1 (3.9)	51	16.6 (4.3)	–5.043§	<0.001

*Trials conducted in mainland China, Hong Kong, and Taiwan.

† Trials conducted outside of mainland China (eg, Japan, United States, Australia, Korea, and United Kingdom).

‡ Independent samples *t* test.

§ Analyses were performed using the Wilcoxon rank sum test because homogeneity of variance assumptions was not met.

taste indistinguishably from the trial preparation while pharmacologic action and toxicity were absent, aims to eliminate bias caused by psychological factors in researchers, subjects, and evaluators during the assessment of the effectiveness of drugs.[23]

The scientific rigor and ethics of placebo-controlled trials were assessed using some self-designed indices, which included the number of trials acceptable to use placebo alone, basic interventions of diseases, emergency plan against aggravated disease conditions, informed consent obtained from subjects, and ethics committee approval. The Guideline 11 proposed by the Council for International Organizations of Medical Sciences in October 2002[24] was used to judge the ethical acceptability of placebo application.

Data Extraction

All included trials were classified into 2 groups: Chinese (conducted in mainland China, Hong Kong, and Taiwan) and non-Chinese (eg, Japan, United States, Australia, Korea, and United Kingdom) trials. All reviewers were trained at the Chinese Evidence-Based Medicine/Cochrane Center, Chengdu, China. Two authors (B.M. and H.-M.Y) assessed each included trial independently. Each item was assigned a *yes* or *no* response depending on whether the item was included in the report. Each *yes* response earned 1 point. Disagreements were resolved by consensus. If needed, a third authors (G.-J.L.) was consulted. The number and percentage of trials reporting each item were calculated, and the difference of each assessment item between the 2 groups was compared. Trial publication date was divided into 3 intervals: phase 1 (≤1999); phase 2 (2000–2004); and phase 3 (2005–2009). We tested the influence of publication date on the number of CONSORT items reported and compared the differences between the 2 groups for each time interval.

Statistical Analysis

Data of normal distribution were presented as mean (SD). All of the statistical analyses were performed by one individual (T.F.) using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, Illinois). Cohen's κ was calculated for interrater reliability on reporting quality assessments. The percentage of trials reporting each item in the 2 groups was compared using the Pearson χ^2 test (the minimum expected count ≥5), continuity correction χ^2 test (1 ≤ the minimum expected count <5), or the Fisher exact test (the minimum expected count <1). The differences in the number of reported CONSORT items for each time interval between the 2 groups were analyzed by *t* test, if the homogeneity of variance assumptions was met or the Wilcoxon rank sum test if it was not. The multiple comparisons of the differences in each group were performed using 1-way ANOVA, followed by a Newman-Keuls post hoc test. $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 905 potentially relevant articles were identified from the initial search, of which 47 duplicate literature and 36 experimental studies were excluded. After examination of titles and abstracts, 58 articles were excluded due to nonclinical research. Another 389 articles that involved CAM other than TCM compound formulations,

herb medicine monomer, or single herb as the intervention group were further excluded. Finally, 375 trials were included, of which 324 were Chinese trials and 51 were non-Chinese trials (**Figure 1**).

Interrater reliability was used to test values from each reviewer and Cohen's κ was 0.721, indicating low interobserver variability.[25] **Table I** outlines the number and percentage of trials reporting each of the 33 modified CONSORT items and the corresponding differences between the 2 groups. The results indicated that the reporting information was inadequate regardless of which group, particularly in terms of clearly defined outcome measures (subitems 8, 9), methods used to enhance the quality of measurements (subitem 10), estimation of sample size (subitem 11), method of random-sequence generation (subitem 12), allocation concealment (subitem 14), implementation of randomization (subitem 15), evaluation of blinding (subitem 17), flow diagram (subitem 20), estimated effect size and its precision (subitems 27, 28), and interpretation of the results (subitems 31, 33). Reporting information was significantly less in Chinese trials compared with non-Chinese trials for the following items: description of scientific background ($P = 0.001$); inclusion and exclusion criteria for participants ($P = 0.034$ and $P = 0.031$, respectively); precise details of the interventions ($P = 0.007$); clear definition of outcome measures ($P < 0.001$); estimation of sample size ($P < 0.001$); allocation concealment ($P = 0.025$); implementation and evaluation of blinding ($P < 0.001$ and $P = 0.025$, respectively); description of statistical methods ($P = 0.008$); flow diagram ($P < 0.001$); intention-to-treat analysis ($P < 0.001$); description of adverse events ($P = 0.005$); and interpretation and generalizability of the results ($P < 0.001$ and $P = 0.029$, respectively).

The mean (SD) number of CONSORT items reported across all Chinese trials was 13.1 (3.9) or 39.7% of the 33 items, while that of non-Chinese trials was 16.6 (4.3) or 50.2%. Comparisons of the mean number of CONSORT items reported for each time interval between the 2 groups are presented in **Table II** and shown in **Figure 2**. The Q statistic was used to compare all pairs of means following 1-way ANOVA. Multiple comparisons with the Q statistic revealed that, in Chinese trials, there were no significant differences in the mean number of CONSORT items reported between phases 1 and 2 (P = NS), but phase 3 significantly increased compared with phases 1 and 2 ($P < 0.05$). In non-Chinese trials, there was no significant difference between phases 2 and 3 (P = NS), but both were significantly increased compared with phase 1 (both, $P < 0.05$). The mean number of CONSORT items reported in the included articles all increased over time regardless of group, and for each time interval, the mean number of items reported in Chinese articles was significantly less than that reported in non-Chinese articles ($P < 0.05$). However, the mean number of items reported in Chinese articles grew continuously, whereas in non-Chinese articles it grew rapidly before 2004, but relatively slower after 2004. Moreover, compared with non-Chinese articles from 2000 to 2004, contemporaneous Chinese articles lagged far behind in terms of the mean number of reported CONSORT items, but the difference decreased after 2005.

Table III shows the assessment outcomes of TCM characteristic indices and other indices that should be reported in placebo-controlled trials. The reported information

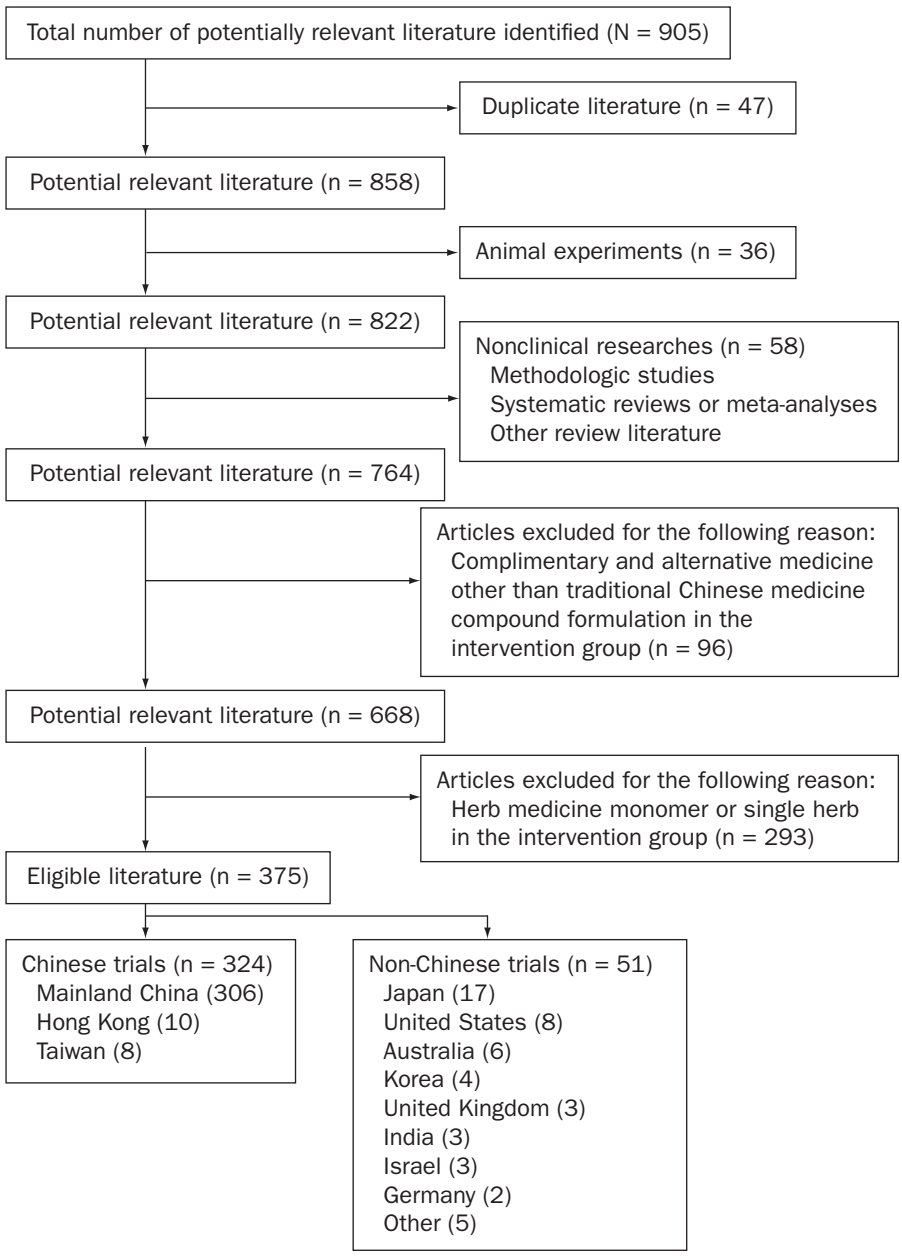

Figure 1. Flow chart showing the article selection process and reasons for exclusion.

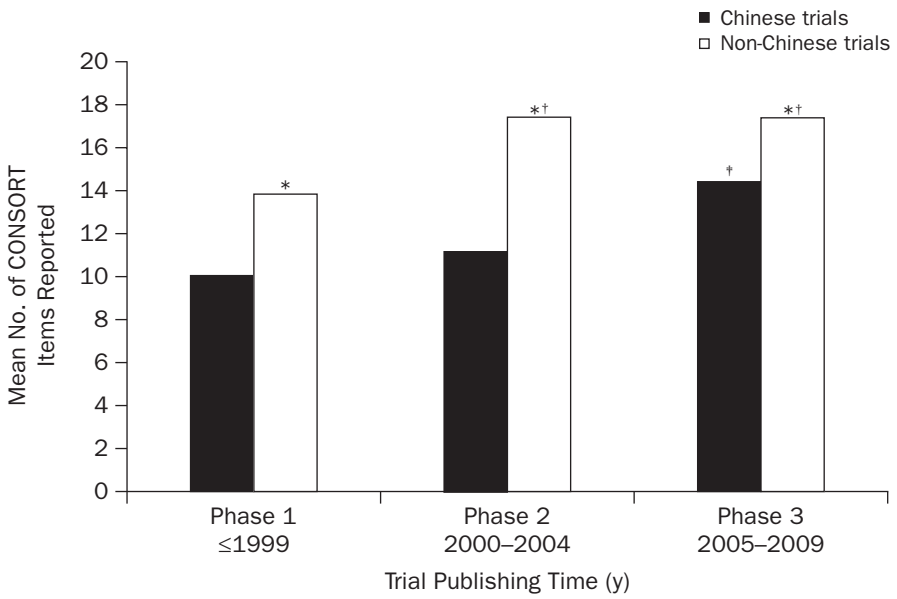

Figure 2. The mean number of Consolidated Standard of Reporting Trials (CONSORT) items reported across all publishing time intervals in randomized placebo-controlled trials of traditional Chinese medicine compound formulations. *$P < 0.05$ versus Chinese trials; †$P < 0.05$ versus phase 1; ‡$P < 0.05$ versus phase 1 and 2.

regarding the characteristics of TCM was considered inadequate in both groups. The results indicated significant differences between the 2 groups in certain indices, such as syndrome type and diagnostic criteria of TCM (both, $P < 0.001$), evaluation indices of efficacy for TCM ($P = 0.001$), and interpretation of the results with TCM theories ($P < 0.001$). As for the previously mentioned items, non-Chinese articles had poorer reporting compared with Chinese articles. In contrast, Chinese articles were inferior to non-Chinese articles in terms of quality control surveillance of interventions ($P = 0.021$).

The assessment outcomes of scientific rigor and ethics of placebo-controlled trials are presented in **Table IV**. Emergency plan against aggravated disease conditions was neglected in a large proportion of both Chinese and non-Chinese trials. Non-Chinese trials tended to have a higher quality compared with Chinese trials in regard to certain aspects: informed consent obtained from subjects ($P < 0.001$); ethics committee approval ($P < 0.001$); and estimation of sample size ($P < 0.001$). However, compared with non-Chinese trials, basic interventions of diseases were adopted more frequently in Chinese trials ($P = 0.003$).

DISCUSSION

Regardless of whether studies were conducted in China, a mean of <51% of the necessary items on the modified CONSORT checklist were reported in the published ar-

Table III. Assessment using some indices reflecting characteristics of traditional Chinese medicine (TCM) and other indices that should be reported in placebo-controlled trials.

Items	Chinese Trials,* No. (%) (n = 324)	Non-Chinese Trials,† No. (%) (n = 51)	Statistic Value	*P*
The composition of TCM compound formulation	292 (90.12)	49 (96.08)	1.242†	0.265
Actions and indications of TCM compound formulation and modern pharmacologic evidence of each active ingredient	150 (46.30)	18 (35.29)	2.157§	0.142
TCM syndrome type	137 (42.28)	3 (5.88)	24.957§	<0.001
TCM diagnostic criteria for each disease	113 (34.88)	1 (1.96)	22.564§	<0.001
Evaluation criteria of TCM for therapeutic effects	69 (21.30)	1 (1.96)	10.851§	0.001
Interpretation of the results with TCM theories	208 (64.20)	1 (1.96)	69.181§	<0.001
Quality control surveillance of interventions	11 (3.40)	6 (11.76)	5.329†	0.021
The manufacturing process of placebo and the difference in sensory characteristics between the study preparation and the placebo	203 (62.65)	32 (62.75)	0.000§	0.990
Number and name of trial registration	5 (1.54)	3 (5.88)	2.167†	0.141

*Trials conducted in mainland China, Hong Kong, and Taiwan.

† Trials conducted outside of mainland China (eg, Japan, United States, Australia, Korea, and United Kingdom).

† Continuity correction χ^2 test.

§ Pearson χ^2 test.

ticles. The data of our study are similar to that found by Gagnier et al,[14] who assessed the reporting quality of RCTs of herbal medicine and found that 45.05% of the CONSORT items were reported in these articles. Huwiler-Müntener et al[26] also reported that 60 randomized placebo-controlled trials published in English-language journals from 1985 to 1997 had a mean of 12.5 of the 25 items (50%) on the 1996 CONSORT checklist. Across all included trials of our study, the information reported was inadequate, particularly in Chinese trials. Many trials failed to report the necessary information, especially the method of sequence generation, allocation concealment, implementation of randomization, evaluation of blinding, flow diagram, estimation of sample size, and clear definition of outcome measures.

Randomization, blinding, and establishment of the control group are 3 principles of clinical research design. Patients receiving placebo may seek other treatment, espe-

Table IV. Assessment of the scientific rigor and ethics of placebo-controlled trials of traditional Chinese medicine compound formulations.

Items	Chinese Trials,* No. (%) (n = 324)	Non-Chinese Trials,† No. (%) (n = 51)	Statistic Value	*P*
Trials that may be acceptable to use placebo alone in the control group	198 (61.11)	39 (76.47)	4.470‡	0.035
Basic interventions of diseases	147 (45.37)	12 (23.53)	8.607‡	0.003
Informed consent obtained from subjects	107 (33.02)	47 (92.16)	63.662‡	<0.001
Ethics committee approval	34 (10.49)	42 (82.35)	140.807‡	<0.001
Emergency plan against aggravated disease conditions	20 (6.17)	5 (9.80)	0.441§	0.506
Estimation of sample size	18 (5.56)	18 (35.29)	41.543§	<0.001

*Trials conducted in mainland China, Hong Kong, and Taiwan.
† Trials conducted outside of mainland China (eg, Japan, United States, Australia, Korea, and United Kingdom).
‡ Pearson χ^2 test.
§ Continuity correction χ^2 test.

cially if there is established effective treatment available, and this may lead to biased results. Thus, in placebo-controlled trials, randomization and blinding play more important roles in reducing biases.[22]

RCTs provide the best evidence for efficacy of health care interventions.[19] However, if the method of sequence generation is used erroneously, biased results are easy to generate. The method of random-sequence generation, allocation concealment, and implementation of randomization should be adequately described in the reports of RCTs. Otherwise, readers cannot identify the authenticity and reliability of randomized trials, and the likelihood of bias in group assignment. In our research, 104 (32.10%) of the Chinese articles and 20 (39.22%) of the non-Chinese articles described the specific method of sequence generation; 23 (7.10%) Chinese and 9 (17.65%) non-Chinese articles reported allocation concealment; and 18 (5.56%) Chinese and 7 (13.73%) non-Chinese articles reported implementation of randomization. As in the present study, Linde et al[27] also found that most CAM trials, which were collected for 5 previously published systematic reviews on herbal medicine (*Hypericum* for depression, *Echinacea* for common cold), homeopathy, and acupuncture, did not report the generation of random sequence and adequate method of allocation concealment. Of the 42 trials on herbal medicine, 13 (31%) and 11 (26%) adequately reported the generation of random sequence and method of allocation concealment, respectively.

Blinding is important to reduce the bias of implementation and evaluation. If blinding is done, the success of blinding should be evaluated[22]; if blinding is not done, the reasons for not blinding should be reported.[28] Blinded groups should be

described. Authors should avoid using terms such as "single-blind" or "double-blind" because such terms are not well understood.[29] The results of our study found that blinding was used in 205 (63.27%) of the Chinese trials, whereas it was adopted in 49 (96.08%) of the non-Chinese trials. Only 5 (1.54%) of the Chinese articles and 4 (7.84%) of the non-Chinese articles reported the success of blinding. Another review article also found similar results; 4 (2.1%) of the included 191 randomized placebo-controlled trials from leading general medicine and psychiatry journals assessed the success of blinding.[30]

Although the necessary information reported was inadequate across all of the included trials of our study, the mean number of CONSORT items reported increased over time regardless of whether it was a Chinese or non-Chinese trial. Moreover, the difference in the mean number of CONSORT items reported between Chinese and non-Chinese trials was decreasing. This may be associated with the generalization and application of the CONSORT statement worldwide. The findings were similar to that of Gagnier et al,[14] who also found a significant increase over time in the number of the reported items in RCTs of herbal medicines. For each decade of publication, the mean number of the reported items across trials of a total of 42 items was as follows: 1970s (12 of the 42 items); 1980s (15); 1990s (18.5); and 2000s (20).

Patients experiencing the same disease may manifest different TCM syndrome types.[31] From the view of TCM, diagnosis and treatment of diseases combined with syndrome differentiation are vitally important. If syndrome differentiation was ignored in any TCM therapies, the therapeutic effect would be affected. In this study, 137 (42.28%) of the Chinese articles reported TCM syndrome type, 113 (34.88%) reported TCM diagnostic criteria of diseases, and 69 (21.30%) reported evaluation indices of efficacy for TCM, whereas in non-Chinese articles, only 3 (5.88%) reported TCM syndrome type and 1 (1.96%) reported TCM diagnostic criteria of diseases and evaluation indices of efficacy for TCM. Whether the articles were Chinese or non-Chinese, the reported information regarding the characteristics of TCM was inadequate. Many investigators only paid attention to the diagnosis criteria and efficacy evaluation indices of Western medicine, but neglected syndrome differentiation and evaluation indices of TCM for therapeutic effects. As for the TCM characteristic indices, the reporting quality of Chinese trials was significantly better than that of non-Chinese trials, which may be related to the fact that TCM originates in China. It is important to conduct TCM research in line with relevant international practice. At present, one of the best methods may be to combine the concept of diseases (defined by Western medicine) with that of syndrome type (defined by TCM) in the diagnosis and treatment of diseases.[32]

In placebo-controlled trials, placebo should be designed to smell, appear, and taste indistinguishably from the trial preparation.[23] However, due to the unique sensory characteristics of Chinese herbal medicine, it is difficult to make a perfectly matching placebo, which makes it easily identifiable. Although capsules may reduce the difference between the study medication and the placebo, the use of capsules is limited because of certain factors, such as change of efficacy and characteristics of drugs.[33] As shown in the present study, 203 (62.65%) of the Chinese articles described the manu-

facturing process of placebo and the difference in sensory characteristics between the study preparation and the placebo; 165 provided only a brief description. Of the non-Chinese articles, 32 (62.75%) reported this item; 15 provided only a brief description. In a large number of trials, it was difficult to determine whether the herbal medications could resemble placebo in all aspects.

The placebo satisfied the criteria of application (ie, the scientific rigor of placebo application). For the standard of placebo application, the Declaration of Helsinki has been amended 6 times, raising various controversies.[34] Smoak[35] pointed out that, generally, subjects in the control group should receive an established effective intervention. For example, regardless of the trial or control group, patients with coronary artery disease should receive oral or intravenous nitrates, β-blockers, anticoagulants, and/or calcium channel blockers according to the state of illness. Use of placebo may be acceptable when there is no established effective intervention; when withholding effective intervention would mostly expose subjects to temporary discomfort or delay in relief of symptoms; when use of effective intervention would not yield scientifically reliable results; and when the use of placebo would not add any serious or irreversible harm to the subjects.[24] In this study, we found that it was unethical to use placebo alone in 38.89% of the Chinese trials and 23.53% of the non-Chinese trials. Additionally, basic interventions were not administered for the treatment of diseases in 177 (54.63%) of the Chinese trials and 39 (76.47%) of the non-Chinese trials. The lack of basic interventions in some organic diseases that had well established measures available, such as coronary heart disease, hypertension, cerebral infarction, asthma, and chronic heart failure, might result in serious or irreversible harm. Although results can be obtained from these trials, the requirement of placebo application could not be satisfied, which were contrary to the scientific rigor of placebo application.

Furthermore, the application of placebo without pharmaceutical intervention involves some ethical issues. All trials must follow the principle of maximum benefit with minimum harm. In placebo-controlled trials, the people involved are consenting volunteers.[36] The contents regarding the ethics of placebo should include receiving institutional review board approval and obtaining informed written consent from all participating subjects. Additionally, in order to protect the safety and interests of subjects, it is essential that an emergency plan be formulated before the test. Through this way, effective measures can be taken to minimize harm in case of emergency or aggravated disease conditions. The results of our study found that institutional review board approval and informed written consent were obtained in 34 (10.49%) and 107 (33.02%) of the Chinese trials, respectively, while they were obtained in 42 (82.35%) and 47 (92.16%) of the non-Chinese trials. The estimation of sample size can also reflect the ethics of placebo application because it can avoid subjecting an excess number of patients to poor efficacy. In the present study, 18 (5.56%) Chinese and 18 (35.29%) non-Chinese articles reported the estimation of sample size.

There are 2 noteworthy limitations of the present study. First, only English- or Chinese-language articles were included. The influence of language of publication on reporting quality is unknown. Therefore, the results of our study are only applicable to English- and Chinese-language reports. Second, research of TCM compound for-

mulations accounted for the majority of the TCM trials in China, while research on Chinese herbal monomer or single-herb treatment accounted for the majority of TCM trials in non-Chinese countries. This led to a great difference in the number of trials between the 2 groups.

CONCLUSIONS

The results indicate that the reporting quality of randomized placebo-controlled trials of TCM compound formulation interventions has improved over time, but still remains poor regardless of country of origin (Chinese or non-Chinese trials). Across all included trials, particularly Chinese trials, the reporting of the items recommended by the CONSORT guidelines was inadequate. The gap in the number of the reported CONSORT items between Chinese trials and non-Chinese trials narrowed over time. Moreover, a large number of trials of TCM, especially non-Chinese trials, lacked syndrome differentiation and the characteristics of TCM. More importantly, in many placebo-controlled trials, especially in Chinese patients, the use of placebo was ethically contradictory and unjustified.

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