

CONSORT Extension for Chinese Herbal Medicine Formulas 2017: Recommendations, Explanation, and Elaboration

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Chinese herbal medicine (CHM) formulas are the major components of traditional Chinese medicine (TCM) interventions. The general reporting quality of randomized controlled trials (RCTs) of CHM formulas is disappointing, although CONSORT (Consolidated Standards of Reporting Trials) Statement extensions for herbal medicinal interventions and acupuncture interventions are available. A group of TCM clinical experts, methodologists, epidemiologists, and editors has developed this CONSORT Extension for CHM Formulas (CONSORT-CHM Formulas 2017) through a comprehensive process, including publication of the draft version, solicitation of comments, revision, and finalization.

The CONSORT 2010 Statement was extended by introducing the idea of TCM *Pattern* and the features of CHM formulas. One new checklist subitem, keywords, was added to facilitate index-

ing and data searching. Seven of the 25 CONSORT checklist items, namely title and abstract, background and objectives, participants, interventions, outcomes, generalizability, and interpretation, are now elaborated, and the explanation of harms specific to CHM formulas is revised. Illustrative examples and explanations are also provided. The group hopes that CONSORT-CHM Formulas 2017 can improve the reporting quality of RCTs of CHM formulas.

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* For a list of contributors to the CONSORT Extension for Chinese Herbal Medicine Formulas (CONSORT-CHM Formulas 2017), see Appendix 1 (available at Annals.org).

Traditional Chinese medicine (TCM), one of the oldest medical systems in the world, is based on its own unique principles and comprehensive theory. Today, it plays an indispensable role in the Chinese health care system, and its impact worldwide is increasing (1). Since the first randomized controlled trial (RCT) of a Chinese herbal medicine (CHM) formula was published in 1982 (2), tens of thousands of clinical reports have been published (3). However, the quality of reporting is not optimal (4–6). Inadequate reporting not only compromises the values of the CHM but also may affect reviewers' and readers' judgments about the efficacy and safety of TCM in general, inviting skepticism and criticism (6). As a result, clinical practice and patient care suffer.

The CONSORT (Consolidated Standards of Reporting Trials) Statement and its extensions have substantially improved the reporting quality of RCTs (7). CONSORT extensions for herbal medicinal interventions (8) and acupuncture interventions (9) have been developed, but neither can be used for reporting clinical trials of CHM formulas, which are the most common interventions in TCM practice. These CONSORT extensions do not adequately take into account the unique characteristics of TCM—theory, principles, formulas, and Chinese medicinal substances (Boxes 1 to 4). Therefore, a new extension has been developed to guide the reporting of trials using CHM formulas.

METHODS FOR THE DEVELOPMENT OF CONSORT-CHM FORMULAS 2017

The development of CONSORT-CHM Formulas (formerly known as CONSORT for TCM) has been a comprehensive process. The first draft of CONSORT-CHM Formulas, including a 22-item checklist and a flow diagram, was published in Chinese (16) and English

(17) in 2007 for open solicitation of comments. Afterward, the draft was disseminated in workshops and academic conferences by executive members of the working group to attract further discussion. Articles on the significance of the CHM formula extension (18), study design rationale (19), CHM formula composition (20), outcome measures (21), adverse effects (22), and further development (23) were published in Chinese or English.

On the basis of the comments and suggestions received, as well as the 2010 version of CONSORT Statement (24), executive members of the working group discussed and revised this extension in Chengdu, China, in late 2012. A consensus meeting, including executive members of working groups, 12 TCM clinical trial experts from China, and 2 herbal medicine experts from Korea, was held in Beijing in June 2013. After the meeting, a further revision was made by executive members and circulated to the working group members. The executive working group finalized the recommendation at the end of 2016.

HIGHLIGHTS OF CONSORT-CHM FORMULAS 2017

CONSORT-CHM Formulas 2017 includes the key concepts of *Pattern* and the features of CHM formulas. With regard to the checklist, compared with CONSORT 2010, CONSORT-CHM Formulas includes 1 new sub-

See also:

Editorial comment

Web-Only

Chinese translations

item, keywords (item 1c). It elaborates on 7 of 25 CONSORT checklist items, namely title and abstract (items 1a and 1b), background and objectives (items 2a and 2b), participants (item 4a), interventions (item 5), outcomes (item 6a), generalizability (item 21), and interpretation (item 22), and it revises the explanation of harms specific to CHM formulas (item 19). The items from the Template for Intervention Description and Replication (TIDieR) are also combined in this extension (25).

The checklist is presented in the **Table**; elaborations of CHM formulas are italicized. Explanations of corresponding items are given below, and available published examples of good reporting are provided in **Appendix 2** (available at Annals.org). There is no modification for the CONSORT flow diagram.

EXTENSION OF CONSORT 2010 TO CONSORT-CHM FORMULAS

Title, Abstract, and Keywords

Item 1a

Standard CONSORT item: Identification as a randomized trial in the title

CHM Formulas extension: Statement of whether the trial targets a TCM Pattern, a Western medicine-defined disease, or a Western medicine-defined disease with a specific TCM Pattern, if applicable

Box 1. Fundamental principles of traditional Chinese medicine theory.

Traditional Chinese medicine (TCM) is a unique and systematic medical system deeply influenced by ancient Chinese philosophy. It believes that the human body is an organic whole, which is closely tied with the universe. Therefore, the activities of nature can affect the human body directly or indirectly. Distinctive theories of *Qi*, Yin-Yang, and the Five Elements commonly used to understand and explain natural phenomena are fundamental to TCM theory (10).

Qi, also translated as “vital energy,” is the basic substance that constitutes the universe. This basic understanding gives rise to the key medical concept in TCM. Yin and Yang are 2 relative opposite manifestations of *Qi*, namely Yang-*Qi* and Yin-*Qi*, and they are opposite and restraint, mutual dependent and supportive, equilibrium and waning, and mutual transformable. The theory of Yin and Yang forms the TCM theoretical structure. The theory of the Five Elements holds that the universe comprises Wood, Fire, Earth, Metal, and Water, and the phenomena of universe come from the movements of and changes in the Five Elements. The interpromoting and interrestraining of the Five Elements are complementary. Promotion and restraint among the Five Elements bear each other, and only in this way can relative harmony and coordination of the internal organs be maintained. These fundamental ideas are especially important for understanding the structure of the body, physiology, and pathology and for guiding clinical diagnosis and treatment in TCM (10).

Box 2. Therapeutic principles of traditional Chinese medicine.

Therapeutic principles are the strategies, based on differentiation of *Pattern*, to determine appropriate treatment and select appropriate medicinal substances to form a formula. The identification of therapeutic principles is highly dependent on the accuracy of *Pattern* differentiation.

Determination of *Pattern* is the basis for developing the therapeutic principles, namely *bianzhenglunzhi*. *Pattern*, also called syndrome or *Zheng*, is a summary of the cause, nature, and location of pathologic changes at a certain stage of disease (11). Traditional Chinese medicine (TCM) practitioners comprehensively analyze all the clinical information collected by the 4 methods of diagnosis—inspection, auscultation and olfaction, interrogation, and palpation—with TCM theory; identify the cause and pathogenesis; and differentiate the diagnosis of *Pattern*. In general, *Pattern* is formed by the elements of “location of disease” and “feature of disease” (12).

Differentiation of *Pattern* is the foundation for identifying therapeutic principles, which is crucial in clinical practice. In a clinical trial, the concept of differentiation of *Pattern* should be carried out throughout the entire process with regard to the rationale of the study design, selection of inclusion and exclusion criteria, formulation of Chinese medicine prescription, selection of outcome measures and data interpretation, etc.

Item 1b

Standard CONSORT item: Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts [26, 27])

CHM Formulas extension: Illustration of the name and form of the formula used, and the TCM Pattern applied, if applicable

Item 1c

New CONSORT item for CHM Formulas extension: Determination of appropriate keywords, including “Chinese herbal medicine formula” and “randomized controlled trial”

Every scientific paper should have a self-explanatory title, a comprehensive abstract, and appropriate keywords (tags readers use to retrieve relevant literature from bibliographic databases). Identifying RCTs of CHM formulas is particularly challenging (3). In general, authors give only the name of the CHM formula and the target disease in the keywords. Different from conventional medicine, the name of a CHM formula can be an English translation, Chinese *Pinyin*, or an acronym. Reader may have difficulties in determining whether the name of the intervention is a Chinese herbal formula. When authors use the general term “Chinese herbal medicine,” they can be referring to a Chinese medicinal component, single herb, or compound formula. This vagueness, inconsistency, and incompleteness impede access to and dissemination of information from clinical trials of CHM formulas and discourage secondary studies. To ensure that a CHM

Box 3. Chinese herbal medicine formulas.

Chinese herbal medicine (CHM) formulas are specific groupings or configurations of Chinese medicinal substances that serve as tools for instituting treatment. The treatment is guided with traditional Chinese medicine (TCM) principles, which is determined by the *Pattern* differentiation (13). If the pattern of a condition is misdiagnosed, the treatment principles will be incorrect, and its derivative formula will be ineffective. Normally, the CHM formula is formed with more than 2 Chinese medicinal substances, although there are formulas with 1 single herb. CHM formulas are the most common interventions in TCM practice.

Preparation forms of CHM formulas include decoctions, granules, pills, tablets, capsules, powders, medicated teas, and medicated wines. Currently, common types of CHM formulas in randomized controlled trials are self-designed formulas and patent proprietary formulas. The former is formulated by the investigators and prepared under the supervision of investigators, for which the composition can be fixed or modified for individual patients. The latter has been manufactured into a fixed-dosage form.

study is appropriately indexed and easily identified, a new CONSORT subitem keywords (item 1c) is recommended. Apart from the name of the intervention, "Chinese herbal medicine formula" and "randomized controlled trial" are recommended keywords.

Background and Objectives**Item 2a**

Standard CONSORT item: Scientific background and explanation of rationale

CHM Formulas extension: Statement with biomedical science approaches and/or TCM approaches

Item 2b

Standard CONSORT item: Specific objectives or hypotheses

CHM Formulas extension: Statement of whether the formula targets a Western medicine-defined disease, a TCM Pattern, or a Western medicine-defined disease with a specific TCM Pattern

The background and underlying rationale of the study design are important to provide in the introduction of a scientific paper. For any study of CHM formulas, whether the rationale is based on biomedical science findings, TCM theory, or both should be elucidated. This section should preferably include a reference to a pilot study or literature review. Moreover, any evidence of the benefits and harms of the CHM formula studied and its active ingredients should also be reported.

The objectives or hypotheses are the questions that the trial is designed to answer. Whether the CHM formula targets a Western medicine-defined disease, a *Pattern*, or a Western medicine-defined disease with a specific *Pattern* should be clarified. Readers can then

easily understand which conditions are targeted in the trial, and the results will be more easily applied in clinical practice.

Participants**Item 4a**

Standard CONSORT item: Eligibility criteria for participants

CHM Formulas extension: Statement of whether participants with a specific TCM Pattern were recruited, in terms of 1) diagnostic criteria and 2) inclusion and exclusion criteria. All criteria used should be universally recognized, or reference given to where detailed explanation can be found.

Pattern plays an important role in determining therapeutic principles. How the *Pattern* is diagnosed and what criteria are used for including and excluding participants should be comprehensively described if the *Pattern* concept is involved in the participant selection. Citing nationally or internationally recognized *Pattern* diagnosis criteria in the study is crucial. Starting from the 1980s, various diagnostic criteria for *Pattern* of specific diseases have been published, such as the Reference Criteria of Deficiency Syndrome Diagnosis (30), the Diagnosis Criteria of Blood Stasis (31), and the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in TCM (32). If standardized diagnostic criteria of *Pattern* are not available, authors should clearly explain how the criteria for their studies were developed and applied in the trial. Such information is necessary for readers to interpret and reproduce the study.

Box 4. Chinese medicinal substances.

Chinese medicinal substances, also referred to as Chinese materia medica, mainly originate from natural sources, including plants, animals, minerals, and some chemical or biological products, that can be raw (fresh or dried) or processed (14). Because most Chinese medicinal substances come from herbal plants, they are commonly called "Chinese herbal medicine."

The properties of Chinese medicinal substances include 5 aspects: Four *Qi*; Five *Tastes*; lifting, lowering, floating, and sinking capabilities; meridian affinity; and toxicity. Four *Qi* refer to cold, hot, warm, and cool of nature. The Five *Tastes* are acrid, sweet, sour, bitter, and salty. Lifting, lowering, floating, and sinking capabilities represent upward, downward, outward, and inward action trends, respectively, on the human body. Meridian affinity indicates which meridian the medical substance acts upon selectively. Toxicity, in the broader sense, means that substances can eliminate the pathogenic factors and preserve health; in the narrower sense, it refers to undesirable efforts (10).

The quality of medicinal substances varies with location of cultivation; parts of collection; season of collection; processing method; and potential contamination with heavy metals, pesticides, or mycotoxins. All of these factors can affect the quality of Chinese herbal medicine formulas, as well as the efficacy and safety assessments of formulas in a clinical trial (15).

Table. Checklist of Items for Reporting Trials of Chinese Herbal Medicine Formulas*

Section/Topic	Item Number	Standard CONSORT Checklist Item	Extension for CHM Formulas	Reported on Page Number
Title, abstract, and keywords	1a	Identification as a randomized trial in the title	<i>Statement of whether the trial targets a TCM Pattern, a Western medicine-defined disease, or a Western medicine-defined disease with a specific TCM Pattern, if applicable</i>	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts [26, 27])	<i>Illustration of the name and form of the formula used, and the TCM Pattern applied, if applicable</i>	
	1c		<i>Determination of appropriate keywords, including "Chinese herbal medicine formula" and "randomized controlled trial"</i>	
Introduction Background and objectives	2a	Scientific background and explanation of rationale	<i>Statement with biomedical science approaches and/or TCM approaches</i>	
	2b	Specific objectives or hypotheses	<i>Statement of whether the formula targets a Western medicine-defined disease, a TCM Pattern, or a Western medicine-defined disease with a specific TCM Pattern</i>	
Methods Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio		
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	<i>Statement of whether participants with a specific TCM Pattern were recruited, in terms of 1) diagnostic criteria and 2) inclusion and exclusion criteria. All criteria used should be universally recognized, or reference given to where detailed explanation can be found.</i>	
	4b	Settings and locations where the data were collected		
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	<i>Description(s) for different types of formulas should include the following: 5a. For fixed CHM formulas 1. Name, source, and dosage form (e.g., decoctions, granules, powders) 2. Name, source, processing method, and dosage of each medical substance. Names of substances should be presented in at least 2 languages: Chinese (Pinyin), Latin, or English. Names of the parts of the substances used should be specified. 3. Authentication method of each ingredient and how, when, where, and by whom it was conducted; statement of whether any voucher specimen was retained, and if so, where they were kept and whether they are accessible 4. Principles, rationale, and interpretation of forming the formula 5. Reference(s) as to the efficacy of the formula, if any 6. Pharmacologic study results of the formula, if any 7. Production method of the formula, if any 8. Quality control of each ingredient and of the product of the formula, if any. This would include any quantitative and/or qualitative testing method(s); when, where, how, and by whom these tests were conducted; whether the original data and samples were kept, and, if so, whether they are accessible. 9. Safety assessment of the formula, including tests for heavy metals and toxic elements, pesticide residues, microbial limit, and acute/chronic toxicity, if any. If yes, it should be stated when, where, how, and by whom these tests were conducted; if the original data and samples were kept; and, if so, whether they are accessible.</i>	

Continued on following page

Table 1—Continued

Section/Topic	Item Number	Standard CONSORT Checklist Item	Extension for CHM Formulas	Reported on Page Number
			<p>10. Dosage of the formula, and how the dosage was determined</p> <p>11. Administration route (e.g., oral, external)</p> <p>5b. For individualized CHM formulas</p> <p>1. See recommendations 5a 1-11</p> <p>2. Additional information: how, when, and by whom the formula was modified</p> <p>5c. For patent proprietary CHM formulas</p> <p>1. Reference to publicly available materials, such as pharmacopeia, for the details about the composition, dosage, efficacy, safety, and quality control of the formula</p> <p>2. Illustration of the details of the formula, namely</p> <p>1) the proprietary product name (i.e., brand name), 2) name of manufacturer, 3) lot number, 4) production date and expiry date, 5) name and percentage of added materials, and 6) whether any additional quality control measures were conducted</p> <p>3. Statement of whether the patent proprietary formula used in the trial is for a condition that is identical to the publicly available reference</p> <p>5d. Control groups</p> <p>Placebo control</p> <p>1. Name and amount of each ingredient</p> <p>2. Description of the similarity of placebo with the intervention (e.g., color, smell, taste, appearance, packaging)</p> <p>3. Quality control and safety assessment, if any</p> <p>4. Administration route, regimen, and dosage</p> <p>5. Production information: where, when, how, and by whom the placebo was produced</p> <p>Active control</p> <p>1. If a CHM formula was used, see recommendations 5a-5c</p> <p>2. If a chemical drug was used, see item 5 of the CONSORT Statement (24)</p>	
Outcomes	6a	Completely defined, prespecified primary and secondary outcome measures, including how and when they were assessed	Illustration of outcome measures with Pattern in detail	
	6b	Any changes to trial outcomes after the trial commenced, with reasons		
Sample size	7a	How sample size was determined		
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomization Sequence generation	8a	Method used to generate the random allocation sequence		
	8b	Type of randomization; details of any restriction (such as blocking and block size)		
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes		
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		

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Table 1—Continued

Section/Topic	Item Number	Standard CONSORT Checklist Item	Extension for CHM Formulas	Reported on Page Number
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome		
	13b	For each group, losses and exclusions after randomization, together with reasons		
Recruitment	14a	Dates defining the periods of recruitment and follow-up		
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group		
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups		
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory		
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms [28])	<i>(There is no extension for this item)</i>	
Discussion				
Limitations	20	Trial limitations; addressing sources of potential bias; imprecision; and, if relevant, multiplicity of analyses		
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	<i>Discussion of how the formula works on different TCM Patterns or diseases</i>	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	<i>Interpretation with TCM theory</i>	
Other information				
Registration	23	Registration number and name of trial registry		
Protocol	24	Where the full trial protocol can be accessed, if available		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		

CHM = Chinese herbal medicine; CONSORT = Consolidated Standards of Reporting Trials; TCM = traditional Chinese medicine.

* The original CONSORT items are provided; elaborations for CHM formulas are in italicized text. We strongly recommend reading this checklist in conjunction with the CONSORT 2010 Explanation and Elaboration (29) for important clarifications on all original items of CONSORT Statement.

Interventions

Item 5

Standard CONSORT item: The interventions for each group with sufficient details to allow replication, including how and when they were actually administered

CHM Formulas extension: Description(s) for different types of formulas should include the following:

5a. For fixed CHM formulas

1. Name, source, and dosage form (e.g., decoctions, granules, powders)

2. Name, source, processing method, and dosage of each medical substance. Names of substances should be presented in at least 2 languages: Chinese (Pinyin), Latin, or English. Names of the parts of the substances used should be specified.

3. Authentication method of each ingredient and how, when, where, and by whom it was conducted; statement of whether any voucher specimen was retained, and if so, where they were kept and whether they are accessible

4. Principles, rationale, and interpretation of forming the formula

5. Reference(s) as to the efficacy of the formula, if any
6. Pharmacologic study results of the formula, if any
7. Production method of the formula, if any
8. Quality control of each ingredient and of the product of the formula, if any. This would include any quantitative and/or qualitative testing method(s); when, where, how, and by whom these tests were conducted; whether the original data and samples were kept, and, if so, whether they are accessible.
9. Safety assessment of the formula, including tests for heavy metals and toxic elements, pesticide residues, microbial limit, and acute/chronic toxicity, if any. If yes, it should be stated when, where, how, and by whom these tests were conducted; if the original data and samples were kept; and, if so, whether they are accessible.
10. Dosage of the formula, and how the dosage was determined
11. Administration route (e.g., oral, external)

5b. For individualized CHM formulas

1. See recommendations 5a 1-11
2. Additional information: how, when, and by whom the formula was modified

5c. For patent proprietary CHM formulas

1. Reference to publicly available materials, such as pharmacopeia, for the details about the composition, dosage, efficacy, safety, and quality control of the formula
2. Illustration of the details of the formula, namely 1) the proprietary product name (i.e., brand name), 2) name of manufacturer, 3) lot number, 4) production date and expiry date, 5) name and percentage of added materials, and 6) whether any additional quality control measures were conducted
3. Statement of whether the patent proprietary formula used in the trial is for a condition that is identical to the publicly available reference

5d. Control groups

Placebo control

1. Name and amount of each ingredient
2. Description of the similarity of placebo with the intervention (e.g., color, smell, taste, appearance, packaging)
3. Quality control and safety assessment, if any
4. Administration route, regimen, and dosage
5. Production information: where, when, how, and by whom the placebo was produced

Active control

1. If a CHM formula was used, see recommendations 5a-5c
2. If a chemical drug was used, see item 5 of the CONSORT Statement (24)

Chinese herbal interventions are always in the form of formulas with multiple medical substances. The reproducibility of a CHM formula highly depends on whether the substances and related authentication,

modification, processing, and production are reported in enough detail. Otherwise, the whole study cannot be replicated by other researchers (33). Therefore, item 5 (interventions) is revised to include the reporting recommendations for common types of CHM formulas (fixed, individualized, and patent proprietary) and their controls (placebo and active). Also, the TIDieR checklist items were embedded (25). Readers can follow the reporting items for each type of CHM formulas one by one.

In addition, quality control methods used for the substances and preparation of the formula should be reported and should detail any references used, such as pharmacopoeias from different countries and regions. The Chinese pharmacopoeia is an official monograph citing the preparation details and quality control of 2165 crude Chinese medicinal substances, patent proprietary drugs, extracts, and others (34). The Japanese pharmacopeia records the methods of preparations and quality control of 148 formulations (mainly herbal extracts) (35). These are important references that authors can cite in reporting the details of CHM formulas used in RCTs.

The choice of control group affects the conclusions that can be drawn from the study, such as whether the outcomes are caused by the treatment effects, the natural progression of the disease, observer or patient expectations, or any other potential influences (36). Among these, placebo design of CHM formulas has been the topic of lively discussion for years. Designing a placebo similar to the formula product with identical color, smell, taste, and texture yet without active properties is not only a science but also an art (36). Transparently reporting the name and amount of each ingredient; processing method; quality control and safety assessment; administration route, regimen, and dosage; and success of masking (if applicable) are essential for readers to assess the validity of study results and to be able to duplicate the study protocol.

We emphasize that the information about quality, safety, and efficacy of CHM formulas should be reported in detail. A complete description helps readers to easily understand the results of a trial. Any novel application of a fixed or patent proprietary CHM formula for conditions different from those traditionally treated, should be well-illustrated by providing the underlying rationale and supporting evidence. Further, we understand that some items in the checklist, especially quality control methods, are not easily achieved at the current stage. By making the reporting recommendation more practical, we allow a compromise proposal with "if any," but it does not mean that these items are not crucial. From the beginning of trial preparation, efforts should be made to produce the highest-quality study in every aspect, including the preparation of CHM interventions. Following these guidelines will make the trial transparent, secure the safety of participants, and thereby increase the scientific value of the trial results.

Outcomes

Item 6a

Standard CONSORT item: Completely defined, pre-specified primary and secondary outcome measures, including how and when they were assessed

CHM Formulas extension: Illustration of outcome measures with Pattern in detail

Valid and reliable outcome measures are prerequisites to justify any conclusion regarding the efficacy and safety of an intervention. Commonly used indices for outcome measures in an RCT of a CHM formula can be categorized into Western medicine-specific outcomes and TCM-specific outcomes (21). The former is often measured using objective biomedical indices, such as blood tests, blood pressure measurements, and radiographs. The latter is more likely to include symptoms and signs assessed by TCM diagnostic methods. Outcome measures and symptoms and signs, as well as *Pattern*, can be measured in terms of occurrence (for example, presence or absence of an individual symptom or sign), by a rating scale (for example, 7-point ordinal scale) (37) or a validated *Pattern* assessment questionnaire (38). In addition, how and by whom the outcomes with *Pattern* are assessed should be reported. All methods used to enhance the quality of measurement should be reported. Supporting references, underlying rationales, and details of assessment procedures must be clearly described.

Harms

Item 19

Standard CONSORT item: All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms [28])

CHM Formulas extension: (There is no extension for this item)

It is widely and mistakenly assumed that Chinese medicinal substances originating from natural sources are harmless. Therefore, harms are less emphasized in RCTs of CHM formulas (16). In general, adverse effects derive from unpredictable adverse events, improper use, contamination, misidentification, and drug-herb interactions (23). For CONSORT-CHM Formulas, any harms or suspected harms of a formula should be reported and explained in terms of TCM theory, biomedical science, or both. Second, outcome measures specific to safety assessment should be addressed. Third, the rationale for selection and the specific assessment methods should be defined with supporting references. Fourth, the details of all adverse events (such as time of occurrence, frequency, severity, or number of patients who withdraw or reduce their doses) should be reported. If no adverse events are reported, the author should state so ("no adverse events were re-

ported"). Finally, in the event of any adverse effects, interpretation about the potential underlying cause is recommended.

Generalizability

Item 21

Standard CONSORT item: Generalizability (external validity, applicability) of the trial findings

CHM Formulas extension: Discussion of how the formula works on different TCM Patterns or diseases

Each CHM formula is determined on the basis of *Pattern* differentiation. The same method of treatment can be applied to patients with different diseases but with the same *Pattern*. On the other hand, different CHM formulas can be applied to patients with the same disease but with different *Patterns*. Therefore, the applicability of trial findings to different *Patterns* of the same disease or the same *Pattern* manifested as different diseases can further be discussed.

Interpretation

Item 22

Standard CONSORT item: Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

CHM Formulas extension: Interpretation with TCM theory

Pattern is the core of TCM theory and the effectiveness of a formula depends on the accuracy of *Pattern* differentiation. Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence in terms of *Pattern* is crucial. Most important, because the formula is designed on the basis of the *Pattern*, its application should follow the *Pattern* differentiation.

DISCUSSION

Several CONSORT extensions have been developed, covering aspects of design, data, and intervention (www.consort-statement.org/extensions). CONSORT-CHM Formulas is developed to expand CONSORT by applying the principles of transparency, consistency, and full disclosure in the use of CHM formulas in RCTs.

The checklist of CONSORT-CHM Formulas was completed through extensive consultations with and solicitation of comments from epidemiologists, journal editors, clinical research methodologists, and TCM clinicians for over a decade. Concerns about the checklist were raised from others in the field. In December 2016, searches of the China Academic Journals Full-text Database and PubMed with "CONSORT for TCM" or "Consolidated Standards of Reporting Trials for Traditional Chinese Medicine" yielded 141 articles related to the

draft version of CONSORT-CHM Formulas. Of these, 24 systematic reviews had used the checklist to appraise the quality of included studies, and 70 articles had cited or supported adherence to the draft when reporting RCTs of CHM formulas.

We understand that all requirements set in the extension may not be easy to meet at this stage. We emphasize that all items are critically related to the quality of RCTs with CHM formulas. Trial quality relies on design, implementation, and reporting. Therefore, researchers are expected to do their best, starting from the study design, preparation, and implementation, not only the final reporting stage.

The value of a recommendation ultimately depends on its use. The CONSORT Statement has achieved great success in encouraging implementation of research-based recommendations, ensuring changes in practice and improving the general quality of RCTs. For better dissemination of CONSORT-CHM Formulas, specific strategies are indispensable. We hope to introduce the extension to all TCM practitioners, researchers, peer reviewers, and journal editors through medical programs, workshops, and conferences. At the same time, the working group welcomes and collects comments and feedback from those in research or clinical practice in order to revise CONSORT-CHM Formulas and keep it relevant. Further, journals can play an important role if they endorse the use of CONSORT-CHM Formulas. Journals wanting to do so can use the following language in their instructions to authors: “[journal name] requires a completed CONSORT-CHM Formulas checklist as a condition of submission when reporting the results of clinical trial of CHM formula(s). Templates can be found at the CONSORT Web site (www.consort-statement.org/consort-statement/). You should ensure that your article, at a minimum, reports content addressed by each item of the checklist.” Funding agencies can require the final report of a clinical trial to follow the recommendations of CONSORT-CHM Formulas. Finally, special grants or awards can be created for high-quality RCTs of CHM formulas adhering to the extension as well.

CONSORT-CHM Formulas 2017 expands the original CONSORT 2010 by applying its principles to the design, execution, and reporting of RCTs of CHM formulas. We hope that these recommendations will promote better reporting and influence design methods of RCTs testing CHM formulas. CONSORT-CHM Formulas 2017 will be periodically reappraised and further modified to ensure that it always serves investigators doing clinical research of CHM formulas.

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APPENDIX 2: AVAILABLE PUBLISHED EXAMPLES OF GOOD REPORTING OF CHM FORMULAS

Title, Abstract, and Keywords

Item 1a: Statement of whether the trial targets a TCM Pattern, a Western medicine-defined disease, or a Western medicine-defined disease with a specific TCM Pattern, if applicable

Example

Efficacy of Zhenjingdingzhi decoction in treating insomnia with Qi-deficiency of heart and gallbladder: a randomized, double-blind, controlled trial. (39)

Item 1b: Illustration of the name and form of the formula used, and the TCM Pattern applied, if applicable

Example

Objective: To evaluate the clinical efficacy of Zhenjingdingzhi decoction in treating insomnia with Qi-deficiency of heart and gallbladder. (39)

Item 1c: Determination of appropriate keywords, including "Chinese herbal medicine formula" and "randomized controlled trial"

Example (There is no available literature with keywords "Chinese herbal medicine formula" and "randomized, controlled trial")

Background and Objectives

Item 2a: Statement with biomedical science approaches and/or TCM approaches

Example

In Chinese medicine, the primary syndrome type of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is phlegm-heat obstructing the lungs. The actions of Xuan Bai Cheng Qi formula are to clear lung heat and dissipate phlegm, so for this reason it is commonly prescribed for AECOPD. . . . Xuan Bai Cheng Qi is a classical prescription dating to the Qing Dynasty (late 1700s) text Systematic Differentiation of Warm Pathogen Diseases by Wu Jutong. Our previous studies found that Xuan Bai Cheng Qi improves oxidant/antioxidant imbalance, pulmonary inflammation in the rat model of COPD. Clinical studies have postulated that Xuan Bai Cheng Qi is effective as a supplementary remedy for treating AECOPD or respiratory failure. (40)

Item 2b: Statement of whether the formula targets a Western medicine-defined disease, a TCM Pattern, or a Western medicine-defined disease with a specific TCM Pattern

Example

We performed a multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of Xuan Bai Cheng Qi in the treatment of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) of the syndrome type phlegm-heat obstructing the lungs. (40)

Participants

Item 4a: Statement of whether participants with a specific TCM Pattern were recruited, in terms of 1) diagnostic criteria and 2) inclusion and exclusion criteria. All criteria used should be universally recognized, or reference given to where detailed explanation can be found.

Example

Patient selection and diagnostic criteria . . . The TCM standard for diagnosing syndromes was worked out with reference to the standard for diagnosing the type of liver stagnation and spleen deficiency in the guidelines of diagnosing and treating functional dyspepsia. Major symptoms are stomach pain or discomfort and anorexia and loose stools. Minor symptoms include: (1) abdominal distention and pain; (2) impatience; (3) insomnia and dreamful sleep; (4) belching and acid reflux; (5) physical and mental fatigue; and (6) abdominal distention after eating. Patients with all the major symptoms and two or more minor symptoms were diagnosed as suffering from the syndrome of liver depression and spleen deficiency. . . . Inclusion and exclusion criteria . . . To be included in the study, patients had to meet the following inclusion criteria . . . (41)

Interventions

Item 5: Description(s) for different types of formulas should include the following:

5a. For fixed CHM formulas

1. Name, source, and dosage form (e.g., decoctions, granules, powders)

Example

Our group developed a Chinese herbal formula Yishen Huazhuo decoction (YHD) to treat mild Alzheimer's disease (AD) . . . (42)

2. Name, source, processing method, and dosage of each medical substance. Names of substances should

be presented in at least 2 languages: Chinese (Pinyin), Latin, or English. Names of the parts of the substances used should be specified.

Example

The treatment group received ShengJinRun-ZaoYangXue granules . . . Maidong 10 g (Dwarf Lilyturf Tuber, *Raidix Ophiopogonis*), Shihu 10g (*Dendrobium*, *Herba Dendrobii*) . . . and Zhigancao 6 g (Prepared Liaurice Root, *Radix Glycyrrhizae preparata*). (43)

3. Authentication method of each ingredient and how, when, where, and by whom it was conducted; statement of whether any voucher specimen was retained, and if so, where they were kept and whether they are accessible

Example

All crude herbal materials were obtained from a local company of herbal supply. The identity of each herbal material, including habitat, harvest seasons, and the preparation of crude material, were authenticated by a senior Chinese herbalist. A sample specimen was kept in Department of Psychiatry, the First Hospital of Xian Jiaotong University. (44)

4. Principles, rationale, and interpretation of forming the formula

Example

Zhenjingdingzhi decoction was extracted by the late Professor Jianhua Hu, Shanghai famous specialist of TCM, originating from the therapy theory of tranquilizing mind by nourishing the heart. It was based on the famous prescription Ganmaidazao decoction from Prescriptions of the *Jin Kui Yao Lue*•*Fu Ren Za Bing* of Zhang Zhongjing, adding Danshen (*Radix Salviae Miltiorrhizae*). . . . Danshen (*Radix Salviae Miltiorrhizae*) has the property of nourishing blood and tranquilizing mind. . . . Compatibility of all the medicine makes therapeutic effect on nourishing heart, tranquilizing, mind, resuscitation and relieve stasis. (39)

5. Reference(s) as to the efficacy of the formula, if any

Example

Our own and prior studies suggest the potential efficacy of Chinese herbal medicine (CHM) for IBS. By their complex pharmacologic nature CHM formulations offer a novel approach by addressing the multifactorial nature of IBS. (45)

6. Pharmacologic study results of the formula, if any

Example

Modern pharmacologic research shows that saikoside has anti-inflammatory, immunoregulatory and liver protective functions, but can also inhibit cholinesterase, act as a quasinicotine sample and adjust the digestive and nervous systems. . . . White *atractylodes rhizome* can activate the muscarinic receptors of the gastrointestinal tract and acetylcholine receptors, and accelerate gastrointestinal motility and evacuation. *Poria cocos* can increase 5-HT levels, indicating that the Xiaoyao pill can alter central monoamine neurotransmitter and hormone levels. . . . (41)

7. Production method of the formula, if any

Example

Xuan Bai Cheng Qi granules . . . produced and packaged by Jiang Yin Tian Jiang Pharmaceutical Co. Ltd. (Jiangsu, China) under good manufacturing practice regulations of China (Approval Number: 0905301-4). Xuan Bai Cheng Qi granules were prepared by decocting the four herbs together, resulting in a concentrated liquid and extraction and capture of the volatile oils. The concentrated liquid was spray-dried on a starch base powder to obtain the final product. Each package of granules was 4.5 g. (40)

8. Quality control of each ingredient and of the product of the formula, if any. This would include any quantitative and/or qualitative testing method(s); when, where, how, and by whom these tests were conducted; whether the original data and samples were kept, and, if so, whether they are accessible

Example 1

Formulation stability and shelf-life testing was conducted across 36 months, ensuring the formulation did not deteriorate (45)

Example 2

The XJXGF formula (Xin-Ju-Xiao-Gao-Fang formula) mainly consists of rhubarb, coptis, semen cassia and citrus aurantium. Abundant compounds within XJXGF have been separated and identified by HPLC chromatography (Fig. 1). The detected compounds include gallic acid, geniposidic acid, verbascoside, naringin, berberine, aurantio-obtusin, aloee-

modin, rhein, emodin, chrysophanol, and physcion. (46)

9. Safety assessment of the formula, including tests for heavy metals and toxic elements, pesticide residues, microbial limit, and acute/chronic toxicity, if any. If yes, it should be stated when, where, how, and by whom these tests were conducted; if the original data and samples were kept; and, if so, whether they are accessible

Example

The finished product was certified to comply with pesticide residue levels, microbiological contaminants, and heavy metals to TGA (Australian Therapeutic Goods Administration) standards. (45)

10. Dosage of the formula, and how the dosage was determined

Example

The dose of 7.5g b.i.d. showed better therapeutic effect than that of 2.5 and 5.0 b.i.d. among 96 subjects (32 per arm) in trial I and was therefore selected for comparison with placebo in trial II. (47)

11. Administration route (e.g., oral, external)

Example

The decoction was used (group A) to soak affected hands and feet, and hot water was added to keep the decoction hotter than 39 °C during soaking, once a day, for 30 min each time, with 7 days as one course. (48)

5b. For individualized CHM formulas

1. See recommendations 5a 1-11

Example (Refer to Examples 5a 1-11)

2. Additional information: how, when, and by whom the formula was modified

Example

The study intervention was planned by the investigator in cooperation with experienced TCM herbalists (Yun Xiao Chen, Kassel, Germany and Andreas Holl, Vienna, Austria). Four expected "clinical patterns" and matching herbal formulae were defined (Table 1). . . . [T]he basic formulae were constituted (7-10 herbs). . . . The exact combination and dosage of herbs in the formulae reflected the clinical opinion and experience of the investi-

gator and the supervising doctors. . . . During follow-up visits, the basic formulae could be substituted for one another or be adapted according to symptoms by adding predefined herbs to the basic formulae (Table 1). (49)

5c. For patent proprietary CHM formulas

1. Reference to publicly available materials, such as pharmacopeia, for the details about the composition, dosage, efficacy, safety, and quality control of the formula

Example

The Jinlida consists of 17 Chinese medicinal herbs, including ginseng, polygonati, atractylo-dis lanceae, sophorae flavescentis, ophiopogon japonicus, rehmanniae, polygoni multiflori, dogwood, poria, perrin, coptis chinensis, anemarrhena, epimedium, salvia, puerariae, semen litchi, and cortex lycii radices. The quality of these herbs and decoction preparation was in accordance with the Chinese Pharmacopoeia (2005). (50)

2. Illustration of the details of the formula, namely 1) the proprietary product name (i.e., brand name), 2) name of manufacturer, 3) lot number, 4) production date and expiry date, 5) name and percentage of added materials, and 6) whether any additional quality control measures were conducted

Example

5-Ling Granule (5-LGr) . . . were prepared by Tasly Pharmaceuticals Inc. (Tianjin, China) (batch no.: 2007B01/2008101 for 5-LGr; . . . The detailed manufacturing procedure of 5-LGr has been posted in the website of the China Patent Inquiry System and carried out in strict compliance with the standards of Good Manufacturing Practice (GMP). Raw weight and ratio of herbal materials of 5-LGr are listed in Table 1. (51)

3. Statement of whether the patent proprietary formula used in the trial is for a condition that is identical to the publicly available reference

Example

Qili qiangxin capsules were approved by China Food and Drug Administration for the treatment of heart failure in 2004. The current study evaluated the effects of qili qiangxin capsules in patients with chronic heart failure. (52)

5d. Control groups

Placebo control

1. Name and amount of each ingredient

Example

An inert placebo was designed matching CHM capsules in size, weight, color, taste, and smell, consisting of cornstarch (80.48%), caramel (11.39%), citric acid (7.10%), coloring (lemon yellow powder [H1794] 0.60% and brown powder [H9885]). (45)

2. Description of the similarity of placebo with the intervention (e.g., color, smell, taste, appearance, packaging)

Example

Both the placebo and herbal tablets were identical in shape, size, color and taste. Furthermore, to minimize the effect of the distinctive smell of herbal preparations on double blinding, the herbal tablets and placebo were all contained in blister packs made from plastic film and aluminium foil, with six tablets in each blister pack. (53)

3. Quality control and safety assessment, if any

Example

Herbs of the control group were routinely examined to be free of contaminants by a professional company (Mag. Ph.R. Kottas-Heldenberg und Söhne, Dragenhandel GesmbH, Vienna, Austria). (49)

4. Administration route, regimen, and dosage

Example

Three bags (15g in granule) and 4.5 bags (22.5g in granule) of 5-LGr or matching placebo granules per day were given to patients aged 5-12 and 13-18 years, respectively. The assigned amount of granules (1 or 1.5 bag) was dissolved into 120-150ml of hot water and taken three times daily. (51)

5. Production information: where, when, how, and by whom the placebo was produced

Example

5-Ling Granule and placebo granules used in this study were prepared by Tasly Pharmaceuticals Inc. (Tianjin, China) (batch no.: 2007B01/2008101 for 5-LGr; 2007C01/2007L01 for placebo granules). (51)

Active control

1. If a CHM formula was used, see recommendations 5a-5c

Example (Please refer to Examples for 5a1 to 5c3)

2. If a chemical drug was used, see item 5 of the CONSORT Statement (24)

Example (Please refer to examples in CONSORT 2010 Explanation and Elaboration [29])

Outcomes

Item 6a: Illustration of outcome measures with Pattern in detail

Example

We assessed each patient's symptoms before and after treatment by means of a rating scale (See Additional File 1), which was completed by the treating physicians when they interviewed their patients before and after treatment (at baseline and week 4). The rating scale consisted of 11 items (2 for the main symptoms, 7 for the accompanying symptoms and 2 for tongue and pulse) with 2 (yes or no) or 4 options (absent, mild, moderate or severe) for each item. Each option was represented by a fixed score, the higher the score, the more severe the symptom, and vice versa. The total score of the rating scale was called syndrome integral. (54)

Harms

Item 19: (There is no extension for this item)

Example (Illustrating all important harms and unintended effects in each group)

Two patients in the maxingshigan-yinqiaosan group had nausea and vomiting. No side effects were observed in the control, oseltamivir, or combination therapy group. No difference in complications after treatment was observed among the 4 groups: 1 case of pulmonary tuberculosis in the control group, 2 cases of pneumonia in the oseltamivir group, 1 case of bronchitis in the maxingshigan-yinqiaosan group, and no complications in the combination therapy group. (55)

Generalizability

Item 21: Discussion of how the formula works on different TCM Patterns or diseases

Example

In TCM, syndromes are the foundations for therapeutic principles, and the same method

of treatment can be applied to patients with the same syndrome, no matter what disease, as defined in Western terms, they have. In the present study, the significance of the syndrome was maintained by recruiting only subjects with not only functional constipation (a disease diagnosed by conventional medicine) but also the "excessive" syndrome (a syndrome pattern diagnosed by TCM). Therefore, the results of this study are useful for making clinical recommendations. (47)

Interpretation

Item 22: Interpretation with TCM theory

Example

Henoch-Schonlein purpura nephritis (HSPN) in children is mainly caused by damp-heat and will further impair spleen and kidney. According to the pathogenesis of HSPN, removing heat, promoting diuresis, nourishing kidney, and consolidating essence can treat HSPN. Considering the physiological and pathological characteristics of child patients, medicinal materials were selected to be slightly purging and nourishing to strengthen body resistance and eliminate pathogenic factors. Chinese herbs were used in this study to treat damp-heat syndrome. After treatment for 4 and 12 weeks, the obvious decline in the total score of damp-heat confirms that Chinese herbs have a good curative effect on alleviating syndromes and signs of damp-heat in the acute stage (within 4 weeks) of the disease. From TCM theory, the accumulation of dampness can affect spleen function and deficiency of spleen Qi causes failure of the body to absorb nutrients. . . . Hematuria is mainly caused by obstruction of collaterals by stasis and heat. The therapy puts more stress on clearing damp-heat and attaches less importance to removing heat from blood, promoting blood circulation, or removing blood stasis. However, this may clarify that internal accumulation of damp-heat is the main syndrome of early-stage child HSPN. With a long course of treatment, the improvement in total score for syndromes and the total effective rate of urinary protein and urinary red cells were higher in the Chinese herb group. This indicates that the internal accumulation of damp-heat is the main cause for lingering illness and the therapy of clearing away heat, promoting diuresis, and removing heat from blood should be adopted throughout the treatment. (56)

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