

Recommendations for reporting randomized controlled trials of herbal interventions: explanation and elaboration

Joel J. Gagnier^{a,b,*}, Heather Boon^c, Paula Rochon^{a,c}, David Moher^{d,e,f},
Joanne Barnes^g, Claire Bombardier^{a,h}, for the CONSORT Group¹

^aDepartment of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

^bCanadian College of Naturopathic Medicine, Toronto, Ontario, Canada

^cFaculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

^dChildren's Hospital of Eastern Ontario Research Institute, Ottawa, Canada

^eDepartment of Pediatrics, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

^fDepartment of Epidemiology & Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

^gCentre for Pharmacognosy & Phytotherapy, School of Pharmacy, University of London, London, United Kingdom

^hInstitute for Work & Health, Toronto, Ontario, Canada

Accepted 16 December 2005

Abstract

Controlled trials that use randomized allocation are the best tool to control for bias and confounding in trials testing clinical interventions. Investigators must be sure to include information that is required by the reader to judge the validity and implications of the findings in the reports of these trials. In part, complete reporting of trials will allow clinicians to modify their clinical practice to reflect current evidence toward the improvement of clinical outcomes. The consolidated standards of reporting trials (CONSORT) statement was developed to assist investigators, authors, reviewers, and editors on the necessary information to be included in reports of controlled clinical trials. The CONSORT statement is applicable to any intervention, including herbal medicinal products. Controlled trials of herbal interventions do not adequately report the information suggested in CONSORT. Recently, reporting recommendations were developed in which several CONSORT items were elaborated to become relevant and complete for randomized controlled trials of herbal medicines. We expect that these recommendations will lead to more complete and accurate reporting of herbal trials. We wrote this explanatory document to outline the rationale for each recommendation and to assist authors in using them by providing the CONSORT items and the associated elaboration, together with examples of good reporting and empirical evidence, where available, for each. These recommendations for the reporting of herbal medicinal products presented here are open to revision as more evidence accumulates and critical comments are collected. © 2006 Elsevier Inc. All rights reserved.

Keywords: Reporting recommendations; CONSORT statement; Herbal medicines; Randomized controlled trials; Consensus technique

1. Introduction

Randomized controlled trials (RCTs) provide the best evidence for efficacy of healthcare interventions [1]. Carefully planned and well-executed RCTs give us the best estimates of treatment effect and can thus guide clinical decision making [2,3], although trials that lack methodological rigor cause over- or underestimation of treatment effect sizes due to bias or confounding factors [4–9]. Hence,

efforts have been undertaken toward improving the design and reporting of RCTs [1,6,10,11].

Current research suggests that reporting quality of complementary and alternative medicine (CAM) trials is poor [12,13]. Linde et al. [12,14] found that most CAM trials do not describe the generation of the random sequence, an adequate method of allocation concealment, and the number and reasons for drop outs and withdrawals [12]. Moher et al. [9,13] reported that a sample of pediatric CAM RCTs reported less than 40% of the consolidated standards of reporting trials' (CONSORT) checklist items with a 24% increase in the number of checklist items included in reports over time. That is, less than half of all information necessary in the reporting of these trials appeared in their reports. Specifically, only 50% of trials reported

¹ Members of this group are listed in Section 8.

* Corresponding author. 5955 Ontario Street, Unit #307, Windsor, Ontario, Canada, N8S1W6. Tel.: +1-519-974-9690; fax: +1-519-258-2396.

E-mail address: j.gagnier@utoronto.ca (J.J. Gagnier).

how random numbers were generated and 25% if allocation concealment was done [13]. The results suggest that a large proportion of CAM trials have poor reporting quality resulting in difficulties with assessment of internal and external validity [12,13].

Linde et al. (2001) showed that reporting quality may vary across different types of complementary therapies with herbal medicine¹ trials being somewhat superior to homeopathy and acupuncture trials [12], although, several systematic reviews state that trials of botanical medicine still fail to report information necessary to judge internal validity, external validity, and reproducibility [15,16] (Gagnier, JJ., 2003, unpublished data). A study examining the quality of reports of a sample of 206 English language herbal medicine RCTs found that less than 45% of the information suggested within the CONSORT statement was reported [17]. For example, approximately 28% of trials described if the person administering the intervention was blinded to group assignment or not, only 22% described the methods for implementing the allocation sequence, and 21% the method for generating the allocation sequence. Also, reporting quality differed between individual botanical medicines and improved across decades from the 1980s to the 2000s [17]. Furthermore, it has been suggested that trials often do not include detailed information on the herbal product itself [15] (Gagnier, JJ., 2003, unpublished data).

It is known that herbal medicines may vary by part of plant used, time of harvest, active constituent levels, type of extract (aqueous, alcoholic, glycerin), and delivery form. Therefore, results of clinical trials on heterogeneous products may vary considerably even if they are using the same botanical species. Variation in herbal products between trials precludes pooling in systematic reviews of herbal medicines since invalid inferences may result from the combined data [14,15] (Gagnier, JJ., 2003, unpublished data). It is clear that readers, editors, and reviewers require increased transparency in the reporting of RCTs of botanical medicines. Reporting guidelines for controlled clinical trials have been developed.

The CONSORT statement was first published in 1996 and revised in 2001 [7,8]. This statement consists of a checklist and flow diagram to guide writers and reviewers on the information that should be available from published reports of two-group parallel RCTs [7,8]. The CONSORT statement has been endorsed by many leading medical journals, editorial associations, professional societies, and funding

agencies [9]. Since its inception, several extensions of the CONSORT statement have been developed [10,18]. Recently, CONSORT was extended to cluster randomized trials [18] and for trials examining harms [10]. Also, an international group of acupuncture researchers developed a set of recommendations for improving reporting of the interventions in parallel group trials of acupuncture—the Standards for Reporting Interventions in Controlled Trials of Acupuncture or STRICTA [11]. Although not a formal extension of CONSORT, MacPherson et al. [11] described STRICTA as an elaboration of item 4 in CONSORT and suggest STRICTA be used together with CONSORT in reporting acupuncture trials.

In June 2004, an international group of trialists, methodologists, pharmacologists, and pharmacognosists met for a consensus meeting in Toronto, Canada that led to the development of recommendations for the reporting of herbal medicine trials [19] (see Tables 1 and 2). The resulting guidelines amounted to a set of elaborations of current CONSORT items that will aid editors and reviewers in assessing the internal/external validity and reproducibility of herbal medicine trials, allowing an accurate assessment of safety and efficacy.

During the development of the elaborations it became clear that an explanation of the concepts within and underlying the elaborations would aid researchers in planning, conducting, and writing reports of RCTs of herbal medicines. In the current paper, we discuss the rationale and scientific background for each elaboration and provide examples of good reporting for each. Where possible, we discuss empirical evidence for each. It should be noted that each elaboration is an addition to existing CONSORT recommendations. Thus all CONSORT items are first listed in Table 1 and elaborations in Table 2.

2. CONSORT elaborations for trials of herbal interventions

Where necessary, we have elaborated items to describe information suggested in reports of RCTs of herbal medicinal product interventions. When reporting an RCT of an herbal medicine, authors should consider reporting the information outlined in the CONSORT statement in addition to the information suggested in these elaborations. Below, we list original CONSORT items (in normal type) followed by elaborations (in *italicized* text) for RCTs of herbal interventions. Excerpts from trials include information suggested by the CONSORT items and the developed elaborations.

2.1. Title and abstract

Item 1:

How participants were allocated to interventions (e.g., “random allocation,” “randomized,” or “randomly assigned”). The title or abstract, or both should state the herbal medicinal product’s Latin binomial, the part of the plant used, and the type of preparation.

¹ *Herbal medicine*: The terms herbal medicine and herbal medicinal product will be used synonymously throughout this article. Herbal medicines include herbs, herbal materials, herbal preparations, and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations used for medicinal purposes and taken by ingestion, injection, or applied topically. This definition does not include single compounds derived from plants or compounds based on specific constituents of plants. (General guidelines for methodologies on research and evaluation of traditional medicines. 2000. World Health Organization: Geneva.)

Table 1
The CONSORT checklist [1,8]

Standard CONSORT checklist: paper section and topic	Standard CONSORT checklist: item	Descriptor	Reported on page number
<i>Title and abstract</i>	1	How participants were allocated to interventions (e.g., “random allocation,” “randomized” or “randomly assigned”).	
<i>Introduction</i> Background	2	Scientific background and explanation of the rationale.	
<i>Methods</i> Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization Sequence allocation	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification).	
Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	
<i>Results</i> Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the number of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group.	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by “intention-to-treat.” State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
<i>Discussion</i> Interpretation	20	Interpretation of results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.	
Generalizability	21	Generalizability (external validity) of trial results.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

Table 2
Proposed elaborations of CONSORT items for RCTs of herbal medicine interventions^a[19]

Standard CONSORT checklist: paper section and topic	Standard CONSORT checklist: item	Descriptor	Reported on page number
<i>Title and abstract</i>	1	How participants were allocated to interventions (e.g., “random allocation,” “randomized” or “randomly assigned”). <i>Either the title or abstract, or both should state the herbal medicinal product’s Latin binomial, the part of the plant used, and the type of preparation.</i>	
<i>Introduction</i> Background	2	Scientific background and explanation of the rationale. <i>Including a brief statement of reasons for the trial with reference to the specific herbal medicinal product being tested and, if applicable, whether new or traditional indications are being investigated.</i>	
<i>Methods</i> Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected. <i>If a traditional indication is being tested, a description of how the traditional theories and concepts were maintained. For example, participant inclusion criteria should reflect the theories and concepts underlying the traditional indication.</i>	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
	4.A. Herbal medicinal product name	<ol style="list-style-type: none"> 1. The Latin binomial name together with botanical authority and family name for each herbal ingredient; common name(s) should also be included. 2. The proprietary product name (i.e., brand name) or the extract name (e.g., EGb-761) and the name of the manufacturer of the product. 3. Whether the product used is authorized (licensed, registered) in the country in which the study was conducted. 	
	4.B. Characteristics of the herbal product	<ol style="list-style-type: none"> 1. The part(s) of plant used to produce the product or extract. 2. The type of product used [e.g., raw (fresh or dry), extract]. 3. The type and concentration of extraction solvent used (e.g., 80% ethanol, 100% H₂O, 90% glycerine) and the herbal drug to extract ratio (drug:extract; e.g., 2:1) 4. The method of authentication of raw material (i.e., how done and by whom) and the lot number of the raw material. State if a voucher specimen (i.e., retention sample) was retained and, if so, where it is kept or deposited, and the reference number. 	
	4.C. Dosage regimen and quantitative description	<ol style="list-style-type: none"> 1. The dosage of the product, the duration of administration, and how these were determined. 2. The content (e.g., as weight, concentration; may be given as range where appropriate) of all quantified herbal product constituents, both native and added, per dosage unit form. Added materials, such as binders, fillers, and other excipients; e.g., 17% maltodextrin, 3% silicon dioxide per capsule, should also be listed). 3. For standardized products, the quantity of active/marker constituents per dosage unit form. 	
	4.D. Qualitative testing	<ol style="list-style-type: none"> 1. Product’s chemical fingerprint and methods used (equipment and chemical reference standards) and who performed it (e.g., the name of the laboratory used). Whether or not a sample of the product (i.e., retention sample) was retained and if so, where it is kept or deposited. 2. Description of any special testing/purity testing (e.g., heavy metal or other contaminant testing) undertaken. Which unwanted components were removed and how (i.e., methods). 3. Standardization: what to (e.g., which chemical component(s) of the product) and how (e.g., chemical processes or biological/functional measures of activity). 	
	4.E. Placebo/control group	<i>The rationale for the type of control/placebo used.</i>	
	4.F. Practitioner	<i>A description of the practitioners (e.g., training and practice experience) that are a part of the intervention.</i>	
Objectives	5	Specific objectives and hypotheses.	

(Continued)

Table 2
Continued

Standard CONSORT checklist: paper section and topic	Standard CONSORT checklist: item	Descriptor	Reported on page number
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors). <i>Outcome measures should reflect the intervention and indications tested considering, where applicable, underlying theories and concepts.</i>	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification).	
Sequence allocation	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Allocation concealment			
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	
<i>Results</i>	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Participant flow			
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group. <i>Including concomitant medication, herbal, and complementary medicine use.</i>	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by “intention-to-treat”. State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
<i>Discussion</i>	20	Interpretation of results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes. <i>Interpretation of the results in light of the product and dosage regimen used.</i>	
Interpretation			
Generalizability	21	Generalizability (external validity) of trial results. <i>Where possible, discuss how the herbal product and dosage regimen used relate to what is used in self-care and/or practice.</i>	
Overall evidence	22	General interpretation of the results in the context of current evidence. <i>Discussion of the trial results in relation to trials of other available products.</i>	

^a CONSORT items [1,16] are listed in normal text. Proposed recommendations for reports of herbal medicine RCTs are listed in italicized text.

Examples

Title: “A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 761 in a sample of cognitively intact older adults: neuropsychological findings” [20].

Abstract: “This was a randomized, double-blind placebo controlled ... The active treatment group received tablets containing 300 mg of Garlic Powder (Kwai). ... This is equivalent to approximately 2.7 g or approximately 1 clove of fresh Garlic per day” [21].

Explanation

CONSORT item #1 is meant to aid in the indexing and identification of reports of RCTs using electronic databases [1]. Hence, the use of the word “randomized,” “randomly,” or “random allocation” is suggested in the CONSORT statement. Additional language is required in the titles and abstracts of trials of herbal medicinal products.

The practice of evidence-based herbal medicine requires access to the herbal scientific literature. The identification of RCTs of herbal medicinal products requires that the product’s Latin binomial, the part of the plant used, and the type of preparation be reported in the title and/or abstract. This information would allow increased specificity in the indexing and identification of RCTs of particular herbal medicine products or preparations. Some herbal medicinal products have a specific trade name or commercial name.² Where applicable, this name should be listed, together with the Latin binomial of the ingredient herb. When the herbal medicinal product used in the trial is a combination herbal product,³ we suggest listing the product name in the title and the separate herbal medicinal species contained within this product in the abstract. In this way, the title of the trial will not be prohibitively long by listing all separate herbal species’ Latin binomials.

Studies indicate that searching for CAM-related topics is challenging due to the diversity of use of controlled vocabulary and indexing procedures between different databases [22]. It has been suggested that if authors of CAM trials (e.g., botanical medicine trials) report abstracts or titles without reference to standard controlled vocabulary, indexers may not assign appropriate indexing terms for particular studies [22,23]. A further problem arises from indexers not having a sufficient number and variety of

descriptors for CAM interventions [24]. When reporting RCTs of herbal medicinal products, the use of the information suggested for titles and abstracts above will likely lead to improved indexing and retrieval.

3. Introduction

3.1. Background

Item 2:

Scientific background and explanation of the rationale. Including a brief statement of reasons for the trial with reference to the specific herbal medicinal product being used, and if applicable, whether new or traditional indications are being tested.

Example:

The extract of Ginkgo biloba leaves entitled EGb 761 is a complex mixture that is standardized with respect to its flavonol glycoside (24%) and terpene lactone (6%) content [1,2]. These two classes of compounds have been implicated in the beneficial effects of EGb 761 in treating peripheral and cerebral vascular insufficiency, age-associated cerebral impairment, and hypoxic or ischemic syndromes [1,3]. Electron spin resonance (ESR) studies conducted in vitro have shown that EGb 761 is an efficient scavenger of various reactive oxygen species, including superoxide anion radical (O_2^\bullet) and hydroxyl radical (HO^\bullet), and that it also exhibits superoxide dismutase-like activity [4]. Recent in vitro studies with animal models have revealed that the extract may exert an anti-free radical action in myocardial ischemia—reperfusion injury. In these studies [5,6], inclusion of 200 mg/l of EGb 761 in the medium that was used to perfuse isolated ischemic rat hearts significantly improved postischemic recovery, reduced ventricular arrhythmias and enzyme leakage, and lowered the content of spin-trapped oxyradicals in the coronary effluents. Interestingly, antiarrhythmic effects were also observed when animals were treated orally with EGb 761 prior to heart perfusion, but a significant reduction in ventricular arrhythmias could be achieved only with high dosages (100 mg/kg for 10 days) [5]. In addition to these studies conducted with EGb 761 [5,6], numerous other studies with experimental animals have indicated that active reduced forms of molecular oxygen, including O_2^\bullet , HO^\bullet , and hydrogen peroxide (H_2O_2), are involved in the pathogenesis of tissue injury that follows myocardial ischemia—reperfusion [7–10] [25]. ... In the present double-blind study, we tested the cardioprotective efficacy of oral treatment with EGb 761, which is known to have in vitro antioxidant properties [4–6], in patients undergoing CPB surgery by manual palpation [25].

² *Trade name/commercial name:* This is the trademark name given to a specific product of a specific business. Or, an invented or arbitrary adopted name given by a manufacturer or merchant to an article to distinguish it as produced or sold by him (Webster’s 3rd New International Dictionary, Unabridged, Encyclopedia Britannica: Chicago). See also *Proprietary product*.

³ *Combination herbal product:* Is a herbal medicinal product comprised of 2 or more individual herbal species combined or mixed and produced as a single entity.

Explanation

The background of reports of controlled clinical trials partially serves to lay out the rationale of the trial [1] with special reference to the specific intervention under study. There is great heterogeneity in the types of herbal medicinal products available. Two different preparations/products of the same herbal species can have different phytochemical profiles, differing pharmacokinetic properties, etc. Given the variability in products, the rationale should clearly overview the scientific data concerning the specific herbal medicinal product under study (e.g., in the above example EGb 761). Where no clinical trials are available for review, extrapolation from preclinical work (i.e., animal studies, observational studies, case reports, known mechanisms) is acceptable. Where no data on the product are available, previous research on similar products to that being tested in the current trial should be reviewed. This information should be clearly stated and ideally include a description of a systematic review of previous studies using the herbal product [1,26].

Also, if the authors are testing a traditional use, a review of the theory and concepts underlying this indication should be reported. Readers with some relevant knowledge of the area should be able to determine the reasoning for the indication. For example, trials of traditional Chinese medicine (TCM) may choose to test a TCM diagnosis (e.g., liver blood deficiency) and not a Western diagnosis (hepatitis). If this is so, the authors should be explicit in their description of why the particular intervention being tested is indicated. For example,

In traditional Chinese medicine, the “Nei-Kuan” acupoint (EH-6, where EH denotes equilibrium envelope of the heart meridian) has been believed to correlate with the function of the heart (Chuang, 1977). Recently, some investigators (Mah et al., 1992; Hsu et al., 1989) observed that acupuncture at Nei-Kuan can improve left ventricular function in patients with coronary heart disease [27].

Additionally, other data (i.e., clinical trials, animal studies, observational studies, case reports, known/proposed mechanisms) that would aid in creating a rationale, even for this traditional indication, can be described in the background. The assumption is that a rationale can be clearly and explicitly reported and that it may be derived from scientific, empirical, historical,⁴ or traditional⁵ sources.

⁴ *Historical sources:* Texts, writings, etc. refer to reported past uses that may have relied upon clinical observation or other means of gathering data. Usually such references do not cite scientific references, but are collections of previously reported used that have presumably been built up, collected across time by observation.

⁵ *Traditional sources:* To knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures. (<http://www.who.int/medicines/organization/trm/orgtrmdef.shtml>; accessed November 2, 2004.)

4. Methods

4.1. Participants

Item 3:

Eligibility criteria for participants and the settings and locations where the data were collected.

If a traditional indication is being tested, a description of how the traditional theories and concepts were maintained. For example, participant inclusion criteria should reflect the theories and concepts underlying the traditional indication.

Example:

There were altogether 118 cases, which were randomly divided into two groups: The QTG (*Qingluo Tongbi Granules: A Chinese herbal medicine*)-treated group and the control group treated with tripterygium glycosides. In the treated group ($n = 63$), there were 18 males and 45 females, aged from 18 to 65 years with an average of 39.5 ± 16.6 and the disease course ranging 2–22 years averaging 7.5 ± 3.6 years. The cases were graded by X-ray according to the criteria set by the American Association of Rheumatoid Arthritis (ARA), USA: 7 cases were grade I, 30 grade II, and 26 grade III. In the control group ($n = 55$), there were 10 males and 45 females, aged from 18 to 65 years with an average of 38.3 ± 16.7 and the disease course ranging 1–21 years, averaging 6.9 ± 3.1 years. Among them, 15 cases were grade I, 21 grade II, and 19 grade III. The cases in the two groups were comparable in sex, age, disease course, and X-ray grading ($P > 0.05$).

Diagnostic criteria and TCM differentiation criteria: Diagnosis of RA was made according to the ARA criteria revised in 1987. Criteria for TCM differentiation of the type of yin-deficiency and heat in collaterals: burning pain in joints, local swelling, or deformity and rigidity, reddened skin with a hot sensation, low fever, dry mouth, yellow urine, red or dark red tongue with ecchymosis and petechia, thin or yellow and greasy or scanty fur with fissures, fine, rapid and slippery, or fine and rapid pulse.

Included in the study were inpatients and outpatients who were diagnosed to have RA of the type of yin-deficiency and heat in the collaterals (*italicized words added from a previous passage in the manuscript*) [28].

The external validity, generalizability, of a trial is partially dependent on the eligibility criteria of participants [1]. Reporting of eligibility criteria in trials of herbal medicine interventions is often poor. One study found that less than 75% of RCTs of herbal interventions adequately reported eligibility criteria [17]. As a result, determination of generalizability of one quarter of these trials would not be possible from reading the published reports. Trials of herbal medicines that aim to test traditional indications

must be sure to report any eligibility criteria that reflect this.

On a related note, authors may choose to exclude participants with previous use of the specific herbal medicinal product itself. It has been suggested that use of herbal medicinal products prior to trial commencement can lead to increased amounts of adverse effects. A trial of *Tanacetum parthenium* (Feverfew) [29] against placebo for migraine prophylaxis included current use of feverfew as an eligibility criterion. Those in the placebo group experienced more side effects, attributed to a “post-feverfew syndrome,” which is the equivalent of withdrawal effects. Such symptomatic worsening following cessation of long-term feverfew consumption has been reported elsewhere [29]. To date, there is no empirical evidence to suggest that use of an herbal medicine prior to a controlled clinical trial of that same herbal medication biases estimates of treatment effect, although, the use and reporting of eligibility criteria to exclude trial participants with recent use is suggested.

Example:

Anyone with a prior adequate trial of St John’s wort (at least 450 mg/d) for the treatment of depression or those who had taken St John’s wort for any reason in the last month were excluded. To reduce the

potential for including a treatment nonresponsive sample, participants who had failed to respond to a trial of an antidepressant (fluoxetine hydrochloride, 20 mg/d, for at least 4 weeks or the equivalent) in the current episode or who had failed to respond to more than 1 adequate trial of antidepressant in a previous episode were also excluded [30].

It is important that trials of herbal medicines report the settings and locations where the data were collected [1]. The location highlights physical factors (e.g., climate, food sources), economics, geography, and social and cultural factors that may affect the generalizability of a study. As well, research settings may vary greatly in their organization, resources, experience, baselines risk, and physical appearances [1]. One study found that less than 40% of herbal medicine trial reports adequately reported the setting and location of the trial [17]. External generalizability of trial results partially rests on complete reporting of this information.

Item 4:

Precise details of the interventions intended for each group and how and when they were actually administered. *Where applicable, the description of a herbal intervention should include the following:*

4.A. Herbal medicinal product name	<ol style="list-style-type: none"> 1. <i>The Latin binomial name together with botanical authority and family name for each herbal ingredient; common name(s) should also be included.</i> 2. <i>The proprietary product name (i.e., brand name) or the extract name (e.g., EGb-761) and the name of the manufacturer of the product.</i> 3. <i>Whether the product used is authorized (licensed, registered) in the country in which the study was conducted.</i>
4.B. Characteristics of the herbal product	<ol style="list-style-type: none"> 1. <i>The part(s) of plant used to produce the product or extract.</i> 2. <i>The type of product used [e.g., raw (fresh or dry), extract].</i> 3. <i>The type and concentration of extraction solvent used (e.g., 80% ethanol, 100% H₂O, 90% glycerine, etc.) and the herbal drug to extract ratio (drug:extract; e.g., 2:1).</i> 4. <i>The method of authentication of raw material (i.e., how done and by whom) and the lot number of the raw material. State if a voucher specimen (i.e., retention sample) was retained and, if so, where it is kept or deposited, and the reference number.</i>
4.C. Dosage regimen and quantitative description	<ol style="list-style-type: none"> 1. <i>The dosage of the product, the duration of administration, and how these were determined.</i> 2. <i>The content (e.g., as weight, concentration; may be given as range where appropriate) of all quantified herbal product constituents, both native and added, per dosage unit form. Added materials, such as binders, fillers, and other excipients; e.g., 17% maltodextrin, 3% silicon dioxide per capsule, should also be listed.</i> 3. <i>For standardized products, the quantity of active/marker constituents per dosage unit form.</i>
4.D. Qualitative testing	<ol style="list-style-type: none"> 1. <i>Product’s chemical fingerprint and methods used (equipment and chemical reference standards) and who performed it (e.g., the name of the laboratory used). Whether or not a sample of the product (i.e., retention sample) was retained and, if so, where it is kept or deposited.</i> 2. <i>Description of any special testing/purity testing (e.g., heavy metal or other contaminant testing) undertaken. Which unwanted components were removed and how (i.e., methods).</i> 3. <i>Standardization: what to (e.g., which chemical component(s) of the product) and how (e.g., chemical processes or biological/functional measures of activity).</i>
4.E. Placebo/control group	<i>The rationale for the type of control/placebo used.</i>
4.F. Practitioner	<i>A description of the practitioners (e.g., training and practice experience) that are a part of the intervention.</i>

The type of information that is required for a complete description of any intervention is relative to the type of intervention being tested. For trials of surgical interventions, for example, a complete description of the individual performing the surgery may be required [1,31]. For herbal medicines, the above information is required to determine, with specificity, the key characteristics of the product that was used. A complete description of the product will allow determination of its efficacy and safety relative to other products.

There are a wide variety of commercially available products containing herbal medicines [32–34]. In addition, there is great variability in the content of these products [34–40]. Often products do not contain the amount (weight, volume, proportion) of the individual constituents listed on their label [41] or any of the constituents at all. Products containing the same botanical species [e.g., *Hypericum perforatum* (St. John's wort)] often contain varying amounts of the plant's marker/active⁶ constituents. For example, research has shown that commercial products of the following botanical species contain varying levels of their respective constituents: *Hypericum perforatum* (St. John's wort) [42,43], *Camellia sinensis* (Green tea) [41], *Tanacetum parthenium* (Feverfew) [37–39], *Eleutherococcus senticosus* (Siberian ginseng), *Panax quinquefolius* (American/Canadian ginseng) [34], *Hydrastis canadensis* (Goldenseal) [44], and *Paullinia cupana* (Guarana) [45]. As a result, the pharmacological properties and in vitro activities may vary between different products (e.g., Refs. [33,46]). Also, some studies have shown that certain botanical products contain not only varying beneficial constituents, but also varying ones [47,48]. Therefore, it is necessary that authors of trials of herbal interventions completely describe the product used.

4.1.1. Herbal medicinal product name

Example:

The AG (*American Ginseng*) capsules contained 3-year-old Ontario grown, dried, ground AG root (*Panax quinquefolius* L.) supplied by the same supplier, Chai-Na-Ta Corp., BC, Canada. ... This AG was the same commercially available product, but from a different batch than the original [49].

Reports should state the Latin binomial and common name/names together with the authority and family name. Reporting of the Latin binomial and common name was also suggested in item 1. The accepted international code of botanical nomenclature [50] indicates that the scientific naming

⁶ *Active constituent(s)*: Those compounds that are proposed to be responsible for the therapeutic effect attributed to the botanical product. This may be a single constituent or more than one. VS Marker compound: A plant constituent, whether an active constituent or not, that acts as a proxy measurement tool for the full spectrum of compounds in the botanical product. This is typically a single compound.

of botanical species must include a Latin binomial (genus and specific epithet) and the authority name. For example, Genus: *Taraxicum*, Epithet: *officinale*, Authority: Linnaeus. In full, this would result in *Taraxicum officinale* L. (Linnaeus is abbreviated as L. here). The authority identifies who originally described the plant. Common names should also be listed here (e.g., Dandelion, Feverfew, St. John's wort). Alone, common names are not sufficient since different herbal species may have the same common name. For example, *Echinacea* is a common name used for *Echinacea angustifolia*, *Echinacea pallida*, and *Echinacea purpurea*. These plants have heterogeneous biochemical profiles [51].

If relevant, the proprietary product⁷ name (brand name, e.g., Kwai) or the extract⁸ name (e.g., LI 160) and the manufacturer of the product should be reported. Such names are a quick means of identification of the specific herbal product including its contents and manufacturing or production. Alone, these names are not sufficient for the product description.

Authors should also report whether the product is licensed in the region where the trial took place. Specific regulatory bodies award licenses for herbal medicinal products. The regulations for attaining licensing are variable across jurisdictions. Although licensing does not ensure product quality or provide the reader with a sufficient description of the herbal product, it does allow the reader to determine the regulatory status and availability of a specific herbal medicine.

4.1.2. Physical characteristics of the herbal product

Example (raw herb):

The ginseng capsules contained 3-year-old Ontario dried and ground ginseng root (*P. quinquefolius* L.). ... All ginseng and placebo capsules came from the same lot [52].

Example (extract):

...all patients received 1 infusion/day with Ginkgo special extract Egb 761 (batch number: 5242) over 30–60 minutes (1 dry vial in 500 ml isotonic solution). The dry vials contained 200 mg of dry extract from Ginkgo biloba leaves (drug-extract ratio 50:1), ... 12 H₂O in 3 ml solution served as solvent [53].

There must be a complete description of the physical characteristics of the herbal product including the part(s) of the plant contained in the product or extract and the type of product [e.g., raw (fresh or dried) or extract]. The part(s) of the plant included in a product are related to the

⁷ *Proprietary product*: An herbal formulation produced by a specific process that is unique and usually carries with it a patent. These products often have a specific name (eg Kwai).

⁸ *Extract*: A type of herbal product in which a solvent (eg, water, alcohol) has been used to withdraw specific constituents from the original herbal material (eg, raw plant parts).

quantities and types of constituents present [54]. Also, the type of product used should be reported given that different product forms have different types and amounts of constituents [55]. If the product is an extract, the type and concentration of the extraction solvent should be reported (e.g., 80% alcohol, 100% H₂O, 90% glycerine) as well as the plant to plant extract ratio (plant:plant extract; e.g., 2:1). This ratio tells the reader how much of the starting plant material (either by weight or volume) was required to produce a specific amount of the finished extract. The method of authentication of raw material (i.e., how done and by whom) describes how the original material or plant was identified and allows the reader to determine, to some degree, if the raw material for the herbal product was produced from the plant as reported. The lot number of the raw material provides the reader with key information as to where the raw material came from.

4.1.3. Dosage regimen and quantitative description

Example:

The treatment was provided as 252 tablets containing 50 mg of either *Ginkgo biloba* standardized extract LI 1370 (containing 25% flavanoids, 3% ginkgolides, and 5% bilobalides) or placebo (both provided by Lichtwer Pharma). Participants were instructed to take three tablets daily for 12 weeks. The extract and dose of *Ginkgo biloba* were chosen on the basis of the results of previous trials in which this dose of

this extract had been reported to be effective in treating cerebral insufficiency⁵ [56].

Authors of trials of herbal medicines should report the dosage regimen and provide a quantitative description of the herbal product. Information regarding the dosage and duration of the trial are of great importance to replicating trials, establishing efficacy or harm for specific dosages and durations, and for external generalizability [1]. The rationale for dosage and duration of the trial should be clear as unclear reasoning questions the methods of a trial and possibly raises some ethical issues as to why the trial was carried out at all.

The weight or amount of all herbal product constituents, both native and added per dosage unit form (i.e., added materials such as binders, fillers, excipients; e.g., 17% maltodextrin, 3% silicium dioxide per capsule) and the percentage of active/marker constituents per dosage unit form (e.g., 0.3% Hypericin per capsule) should also be reported. This provides the reader with a profile of the quantity of the botanical product constituents.

4.1.4. Qualitative testing

Example:

The content of various ginsenosides (Rg₁, Re, Rf, Rb, Rc, Rb₂, and Rd), which are dammarane saponin molecules found among *Panax* species, was determined in the laboratory of Dr. John T. Arnason at the Department of Biology, Faculty of Science, University of Ottawa, Ontario, Canada, using high-performance liquid chromatography (HPLC) analyses, a method similar to the one developed for the American Botanical Council Ginseng Evaluation Program [27]. A Beckham HPLC system with a reverse-phase Beckham ultrasphere C-18, 5 μm octadecylsilane, 250 × 4.6 mm column was used for the analyses. The ginsenoside standards used for comparison were provided by two sources. Rg₁ and Re were provided by Dr. H. Fong, University of Illinois and Rf, Rb₁, Rc, Rb₂, and Rd were provided by Indofine Chemical Co., Somerville NJ [57].

Table 1
Energy, nutrient, and ginsenoside profile of the American ginseng (*Panax quinquefolius* L.) and placebo capsules

Constituent (per g)	Placebo ¹	Ginseng ¹
Energy ²		
(kJ)	14.68	14.39
(kcal)	3.51	3.44
Macronutrients ²		
Carbohydrate (g)	0.73	0.57
Fat (g)	0.039	0.013
Protein (g)	0.069	0.26
Ginsenosides ³		
(20S)-Protopanaxadiols (%)		
Rb ₁	—	1.53
Rb ₂	—	0.06
Rc	—	0.24
Rd	—	0.44
(20S)- Protopanaxatriols (%)		
Rg ₁	—	0.100
Re	—	0.83
Rf	—	0
Total (%)	—	3.21

Adopted from: 54.

¹ To equate energy and macronutrient values to 1, 2, or 3 g American ginseng, multiply by 1, 2, or 3, respectively. To determine values for placebo, multiply by 2.

² Determined by the Association of Official Analytical Chemists methods for macronutrients [18].

³ Determined by HPLC analyses [20].

Trials should report the product's chemical fingerprint⁹ and methods used (machinery and chemical reference standards) and who performed them (the name of the laboratory used). The fingerprint can be reported in a graph or a table describing the key constituents of the herbal medical product. Chemical profiling, using the proper techniques is essential to providing a clear and accurate report of a product's constituents, and provides both qualitative and quantitative information [58–60]. Bauer and Tittel [61] have provided some guidelines for the characterization

⁹ *Chemical fingerprint*: This is a graphic description of the herbal product constituents by means of an accepted analytical method for that particular botanical product. For example, high-pressure liquid chromatography or gas chromatography may be used.

and standardization of plant material used for pharmacological, clinical, and toxicological studies. Also the Association of Analytical Communities (AOAC) has outlined standards for analyzing specific herbal medicinal products [62] as has the American Herbal Pharmacopoeia produced by the American Botanical Council [63] and the United States Pharmacopoeia [64]. Reports might also describe if a voucher specimen¹⁰ (i.e., retention sample) was retained and if so, where it is kept or deposited, so that independent sources can verify the chemical profile. Herbal medicines are often contaminated [65]. Thus, a complete description of any special testing/purity testing (e.g., heavy metal or other contaminant testing) and the removal of unwanted components (which and how (the methods)) should be included in reports where relevant. All such methods are relevant given that they may alter the composition of the herbal product.

Standardization has been hotly debated in the literature (e.g., [58]). Often, companies or researchers attempt to standardize botanical products to specific chemical “marker” constituents. These “marker” constituents may be considered to be the primary “active” constituents or merely serve as an index of the product’s chemical profile [58]. Although products on the commercial market may not be standardized and often an “active” constituent is not known, if standardization was done in a clinical trial of an herbal product, it should be reported. Authors should report, what the product was standardized to (e.g., which chemical component(s)), how this was done (i.e., chemical processes or biological/functional measures¹¹ of activity) (e.g., Ref. [66]), and the percentage of this particular constituent per dosage unit form.

4.1.5. The rationale for the type of control/placebo used

Example:

The placebo, on the other hand, consisted of identical capsules containing corn flour. The energy, carbohydrate content, and appearance of the placebo were designed to match that of the AG (*American Ginseng capsules*) (italicized words added) [49].

In botanical medicine trials, as in other trials, it is important to have a complete description of the characteristics of the control group and the way in which it was disguised [1]. If a placebo control was used, the placebo should be closely matched to the control intervention [67]. For trials of herbal interventions, the rationale for the type of control/placebo

¹⁰ *Voucher specimen*: Those specimens retained in a collection as representatives of a study, and that are presumed to be accurately identified by competent authorities.

¹¹ *Biological/functional measures of activity*: These are in vitro test procedures that attempt to determine a specific action of an herbal product, so as to act as a proxy for determining product quality. For example, trials of *Tanacetum parthenium* (Feverfew), the activity of the intervention was measured by its’ anti-secretory activity against C-serotonin release from platelets [56].

used should be described. There have been some trials reporting using placebos that are matched to color and smell to the active intervention, but that contain ingredients that are themselves active (e.g., Ref. [68]). If a control group is active, comparisons between it and the experimental group will be affected. While it may be a challenge to construct matched placebos for certain herbal product interventions, it is not impossible.

4.1.6. A description of the practitioners that are a part of the intervention

Example:

To participate in the study, physicians had to (i) be a medical specialist with a degree in internal medicine and general medicine, (ii) have a certified degree in TCM by a German society for medical acupuncture, and (iii) have at least 5 years of practical experience in TCM (according to the German Acupuncture Societies Working Group standard)... The herbal formulations for the TCM group were designed by a herbalist (Carl-Hermann Hempen) and prepared by a pharmacist, both of whom specialize in Chinese herbal medicine (S. Dietz, Franz-Joseph-Pharmacy, Munich, Germany). In addition to the basic formula, every patient received a second additional formula tailored to his or her individual TCM diagnosis (Table 1) [69].

On occasion, a herbal intervention trial may include a healthcare practitioner as part of the intervention. Practitioners have varying levels of training, years of experience, theoretical orientations, and work in different environments. Similar to surgical trials, such trials should provide a description of the practitioners (e.g., training and practice experience) that are a part of the intervention [1].

4.2. Outcomes

Item 6:

Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors). *Outcome measures should reflect the intervention and indications tested considering, where applicable, underlying theories and concepts.*

Example:

All outcome measures were assessed at baseline and after 30 days of treatment at the follow-up visit. The primary outcome measures were changes in quality of life as measured by the Physical and Mental Component Summary scales of the 12-Item Short Form Health Survey (SF-12). The SF-12 is widely used in measuring health and quality of life and has been shown to have a high level of agreement with scores from the original 36-Item Short Form Health Survey (SF-36) [11]. The SF-36 has been

validated in several Chinese studies, whereas evaluation of the SF-12 is ongoing [11]. Secondary outcome measures included assessments of physical performance, memory, sexual function, and *qi*... The *qi* scale is a 17-item instrument (14 items on an interviewer-administered questionnaire and 3 physical examination items) that was developed through an international collaboration of clinical investigators with expertise in scale development and traditional Chinese medicine. Questionnaire items address symptoms commonly included in a traditional Chinese medical interview, including breathing, energy level, appetite, heartburn, sweating, bowel patterns, pain, temperature sensations, sleep habits, and sexual ability. The physical examination items address tongue coating, tongue muscle quality, and pulse quality. The scale was developed for this study and has not been validated. The 14 questionnaire items are scored on a scale of 0–4 points, and the physical examination items are scored on a scale of 0–3. The total *qi* score is the sum of each score, ranging from 0 (best) to 65 (worst) [70].

As with any RCT, outcome measures, both primary and secondary, should be relevant to the indications being tested, be fully reported, and describe any methods used to enhance the quality of measurements [1,8]. When performing RCTs testing herbal interventions, concepts that go beyond Western medical terminology and understanding may be relevant. For example, in the above trial the particular Chinese herbal remedy being tested is purported to increase longevity, quality of life, energy, memory, sexual function, and *Qi*, a Chinese concept that is loosely translated as vital energy. Therefore, in addition to measures of health and quality of life, these investigators required a measure of *Qi* to test the change in vital energy during the course of this trial. Ultimately, to test the function of traditional herbal medicines, we advise that the outcome measures reflect the underlying theories and concepts and therefore the indications for the specific herbal medicine intervention under investigation.

5. Results

5.1. Baseline data

Item 15:

Baseline demographic and clinical characteristics of each group. Including, *concomitant medication use or herbal medicinal product use*.

Example:

Eight patients (mean age 44.9 (SEM 4.2) years) received feverfew and nine (mean age 51.2 (2.3) years) received placebo capsules. The patients in the active group had taken 2.44 (0.2) small leaves of feverfew daily for 3.38 (0.58) years before entry to the study,

and those in the placebo group had taken 2.33 (0.48) small leaves daily for 4.18 (0.67) years. Thus the two groups did not differ in the amount of feverfew consumed daily or the duration of consumption. ...

One patient in each group was taking conjugated equine estrogens (Premarin); the patient in the placebo group was also taking pizotifen. One patient given feverfew was taking the combined oral contraceptive Orlest 21. One patient in each group was taking a diuretic: the patient given feverfew was taking clorazepate and the patient given placebo was also taking a product containing tranlycypromine and trifluorperazine. In addition, two people in the placebo group were taking vitamin preparations and one prochlorperazine [71].

A complete description of participants who entered a trial allows readers and clinicians to assess how relevant the trial is to a specific patient. As a part of the baseline assessments in trials of herbal medicinal products, authors should clearly assess and describe any current medication or herbal product use. Differences between groups on medication or herbal product use may confound results [72].

6. Discussion

6.1. Interpretation

Item 20:

Interpretation of results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes. *Interpretation of the results in light of the product and dosage regimen used*.

Example:

Although EGb 761 is generally used at a dose of 120 mg/day in treating chronic disease states, we chose to administer the extract at more than twice its usual dose, but for only 5 days before the operation, to cope with the enhanced generation of oxidant species that was expected to follow postunclamping procedures. Measurements of DMSO/AFR concentrations indicated that EGb 761 treatment significantly protected plasma ascorbate levels in all sampling sites during the initial 5–10 minutes of reperfusion (see Table 3), a period during which free radical processes are considered to be critical. Analyses of plasma TBARS concentrations revealed that EGb 761 treatment also suppressed (or substantially attenuated) the transcardiac release of MDA, indicating protection against free radical-induced lipid peroxidation. These two findings offer some clues regarding the mechanisms that underlie the protective action of EGb 761 in open-heart surgery. It has been reported that EGb 761 protects the hearts of ischemic

rat against reperfusion-induced decreases in ascorbate [6]. We did not observe any in vitro chemical interaction between EGb 761 and AFR or DMSO/AFR that would have maintained ascorbate levels. Therefore, in performing its antioxidant role, it seems that the extract competes effectively with circulating ascorbate (e.g., by directly quenching oxyradicals once they have been formed). ... [73].

Explanation:

The discussion section of a clinical trial report provides the reader with information to determine the pros and cons of the study and how this study relates to other research in the area. Understanding how the results with this product and dosage regimen relate to the results of other trials with similar or different products or dosage regimens allows the reader to establish a context from which to determine strengths or drawbacks of the specific intervention used. Therefore, authors should clearly state specific aspects of the product or dosage regimen that could have resulted in trial findings.

This concept is discussed here under Item 20, to highlight the necessity of authors of reports of RCTs of herbal products to explicitly consider the product and dosage regimen as potential strengths or drawbacks of the study. Although we have formally separated this from the elaboration under Item 22, discussion of the trial results in the context of the current evidence (Item 22); we admit that these aspects of the discussion section are closely related, and may be written together in the body of the manuscript.

6.2. Generalizability

Item 21:

Generalizability (external validity) of trial results. *Where possible, discuss how the herbal product used relates to what is used in self-care and/or practice.*

Example:

G115 is a standardized ginseng extract, which is often complexed with various other substances and marketed commercially. Ginsana[®], Gericomplex[®], Geriatric Pharaton[®], and ARM229 are several commercial standardized ginseng products that have been studied, and may include some or all of the following substances in addition to G115: vitamins, minerals, trace elements, and dimethylaminoethanol bitartrate.

A word of caution for the consumer. As noted previously, the FDA classifies ginseng as a food supplement, so it is marketed rather extensively in health food stores. An estimated 5–6 million Americans use ginseng products [6]. However Chong and Oberholzer [11] note that there are problems with quality control, and indeed a recent report [12] indicated that of 50 commercial Ginseng preparations assayed, 44

contained concentrations of ginsenosides ranging from 1.9% to 9.0%, while six of the products had no detectable ginsenosides [74].

Generalizability, or external validity, is the extent to which the results of a study hold true in other circumstances [75]. The word “circumstances” here can mean other individuals or groups of individuals, other similar interventions, dosages, timing, administration routes, and other settings for starters. Given the wide variability in herbal medicinal products available on the market, and their variable quality and content, a review of how the products used in the current trial relate to what is available and/or used by consumers and practitioners is quite valuable. This information would allow the reader to determine the availability of products that may act similarly to the one used in the trial. Application of clinical trial results partly relies on the availability of the intervention or a similar intervention.

Item 22:

General interpretation of the results in the context of current evidence. *General discussion of the trial results in relation to trials of other available products.*

Example:

The majority of published studies to date have used a powdered garlic preparation, similar to the preparation method used in this study. Considerable variability in outcomes exists between these studies. For example, Adler et al. [13], using a commercial dehydrated garlic tablet, reported a significant net drop of 13.1% in LDL-C levels relative to the placebo group in 12 weeks, and Jain et al. [15], using the same product and a similar design, reported a significant net decrease of 8% in LDL-C levels in moderately hypercholesterolemic adults. However, three other studies [19,20,22], using the same dosage of the same commercial dehydrated garlic powder product (Kwai[®], Lichtwer Pharmaceuticals) reported no significant effect. The dose of powdered garlic tablets used in the five studies just cited, 900 mg/day, was similar to the full dose of 1000 mg/day used in this study. The allicin content of the tablets used in this study, 1500 mg/day in the full dose, was lower than the amount used in other studies with powdered garlic preparations. Other types of garlic preparations used in lipid lowering trials have included aged garlic extract and teamed garlic oil. Steiner et al. [14] used a large dose, 9 tablets/day, of aged-garlic extract, and reported a statistically significant 4.6% lowering of plasma LDL-C levels. In contrast, a recent study using steamed garlic oil supplementation reported no significant effect on cholesterol levels in hypercholesterolemic adults after 12 weeks [18]. One explanation could be that the oil is not as effective as dehydrated garlic powder because it contains different sulfur-containing phytochemicals [30]. Some of the

discrepancies reported in these studies can be explained by the heterogeneity that exists among them in terms of study design, duration, subject characteristics, adherence, or confounders such as weight, diet, and exercise [76].

Discussing trial results in the context of relevant studies is important to put the trial results in the context of existing empirical evidence [1,77]. Some trials fail to provide the reader with sufficient information to determine how the current results relate to other research. For example, Drew and Davies [56] report that “*Ginkgo biloba* extract LI 1370 had no greater therapeutic effect than placebo in treating tinnitus. In addition, other symptoms of cerebral insufficiency were not significantly affected by the treatment (Table 3). The results from this trial are similar to some reports and contrast with others.² This study differs from other trials in many ways.” (p. 5). This provides the reader with little information from which to judge the efficacy of the product currently tested relative to other products that have been tested. Different botanical products can have different constituents and therefore differing therapeutic effects [34–40].

It is suggested here that discussion sections of trials of botanical interventions include a discussion of the trial results in the context of previous research while offering explicit consideration of the similarities or differences between products used therein. It is inappropriate to support or refute a trial’s results by referring to literature that has tested a different product. Authors should be careful to clearly report when they are drawing inferences between heterogeneous products. When clinical trials on the specific product tested do not exist, preclinical data should be discussed. This includes animal, *in vitro*, and other data.

7. Comments

Randomized allocation is the best tool to control for bias and confounding in controlled trials testing clinical interventions. Investigators must be sure to include in reports of these trials information that is required by the reader to judge the validity and implications of the findings. In part, complete reporting of trials will allow clinicians to accurately appraise studies so as to modify their clinical practice to reflect current evidence. The CONSORT statement was developed to assist investigators, authors, reviewers, and editors on the necessary information to be included in reports of controlled clinical trials. The CONSORT statement is applicable to any intervention, including herbal medicinal products.

Controlled trials of herbal medicines interventions do not adequately report the information suggested in CONSORT. Recently, several CONSORT items were elaborated to become relevant and complete for controlled trials of herbal medicines [19]. We expect that these recommendations will

lead to more complete and accurate reporting of herbal medicine trials.

We wrote this explanatory document to further explain the suggested elaborations and to assist authors in using them. We provide the CONSORT items and the associated elaborations, together with examples of good reporting and empirical evidence, where available. These recommendations for the reporting of RCTs of herbal medicine are open to change and revision as more evidence accumulates and critical comments are collected.

8. Focus group participants

The individuals listed below participated in the premeeting phone calls or attended the consensus meeting and provided input toward the elaborations to existing CONSORT checklist items.

Doug Altman (Cancer Research UK Medical Statistics Group, Centre for Statistics in Medicine, Oxford, UK); Joanne Barnes (Centre for Pharmacognosy and Phytotherapy, The School of Pharmacy, University of London, London, UK); Claire Bombardier—*Meeting Chair* (Department of Health Policy Management and Evaluation, Faculty of Medicine, University of Toronto, Canada); Heather Boon (Leslie Dan Faculty of Pharmacy, University of Toronto, Canada); Mark Blumenthal (American Botanical Council, Austin, TX, USA); Ranjit Roy Chaudhury (Chair INCLEN Inc., India); Philip Devereaux (Department of Clinical Epidemiology and Biostatistics, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada); Theo Dingermann (Institut for Pharmaceutical Biology Biozentrum, University of Frankfurt/Main, Germany); Joel Gagnier—*Meeting Coordinator* (Department of Health Policy Management and Evaluation, Faculty of Medicine, University of Toronto, Canada); Gary Leong (Jamieson Vitamins Inc., Windsor, Ontario, Canada); Allison McCutcheon (Faculty of Pharmaceutical Sciences, University of British Columbia, British Columbia, Canada); David Moher (Children’s Hospital of Eastern Ontario Research Institute, Ottawa, Canada); Max H. Pittler (Complementary Medicine, Peninsula Medical School, University of Exeter, Exeter, UK); David Riley (University of New Mexico Medical School, Santa Fe, New Mexico, USA); Paula Rochon (Baycrest Centre, Toronto, Ontario, Canada); Michael Smith (Health Canada, Natural Health Products Directorate, Ottawa, Ontario, Canada); Andrew Vickers (Memorial Sloan-Kettering Regional Cancer Centre, New York, NY, USA).

The members of the CONSORT Group are listed in the following Website: <http://www.consort-statement.org/profiles/partners.html>.

Acknowledgments

We would like to thank Greer Palloo for aiding in the preparation for the June meeting and Jaime DeMelo and Cyndi Gilbert for assisting Joel Gagnier and Claire Bombardier during the meeting procedures.

This study was funded in part by an operating grant from the Canadian Institutes of Health Research, Clinical Trials Divisions; Grant number: ATF-66679. Dr. Gagnier is supported by a postgraduate fellowship from the Canadian Institutes of Health Research and the Natural Health Products Directorate.

Details of ethical approval: Ethical approval was acquired from the University of Toronto Health Sciences Ethics Review Committee, obtained on January 23, 2004.

References

- [1] Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised consort statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663–94.
- [2] Mulrow CD, Cook DJ, Davidoff F. Systematic reviews: critical links in the great chain of evidence. In: Mulrow C, Cook D, editors. *Systematic reviews: synthesis of best evidence for health-care decisions*. ACP: Philadelphia, PA; 1998.
- [3] Sackett DL, Richardsom WS, Rosenberg W, Haynes B. *Evidence-based medicine: how to practice and teach EBM*. New York, NY: Churchill Livingstone; 1998.
- [4] Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–12.
- [5] Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials: current issues and future directions. *Int J Technol Assess Health Care* 1996;12:195–208.
- [6] Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996;17:1–12.
- [7] Begg CB, Cho MK, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996;276:637–9.
- [8] Moher D, Schulz KF, Altman D, for the CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;285:1987–91.
- [9] The CONSORT Group. Accessed Nov 1, 2004. Available at <http://www.consort-statement.org/endorsements/endorsements.htm>.
- [10] Ioannidis JPA, Evans SJW, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, et al, for the CONSORT Group. Improving the reporting of harms in randomized trials: expansion of the CONSORT statement. *Ann Int Med* 2004;141:781–8.
- [11] MacPherson H, White A, Cummings M, Jobst K, Rose K, Niemtow R. Standards for Reporting Interventions in Controlled Trials of Acupuncture: The STRICTA Recommendations. *Acupunct Med* 2001;20(1):22–5.
- [12] Linde K, Jonas WB, Melchart D, Willich S. The methodological quality of randomized controlled trials of homeopathy, herbal medicines and acupuncture. *Int J Epidemiol* 2001;30:526–31.
- [13] Moher D, Sampson M, Campbell K, Beckner W, Lepage L, Gaboury I, et al. Assessing the quality of reports of randomized trials in pediatric and complementary and alternative medicine. *BMC Pediatrics* 2002;2.
- [14] Linde K, ter Riet G, Hondras M, Vickers A, Saller R, Melchart D. Systematic reviews of complementary therapies—an annotated bibliography. Part 2: Herbal medicine. *BMC Complement Altern Med* 2001;1:5.
- [15] Gagnier JJ, VanTulder M, Bombardier C, Burman B. Botanical medicine for low back pain. *Cochrane Review* (Protocol Published 2003).
- [16] Little C, Parsons T. Herbal therapy for treating rheumatoid arthritis. *Cochrane Library* 2000;4.
- [17] Gagnier JJ, DeMelo J, Bombardier C. Quality of reports of randomized controlled intervention trials of herbal medicines. *Am J Med* 2006 (in press).
- [18] Campbell MK, Elbourne DR, Altman DG, for the CONSORT Group. CONSORT statement: extension to cluster randomized trials. *BMJ* 2004;328:702–8.
- [19] Gagnier JJ, Boon H, Rochon P, Barnes J, Moher D, Bombardier CB for the CONSORT Group. Reporting randomized controlled trials of herbal interventions: an elaborated CONSORT statement. *Ann Int Med* 2006;144:364–7.
- [20] Mix JA, Crews WD. A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 7611 in a sample of cognitively intact older adults: neuropsychological findings. *Hum Psychopharmacol Clin Exp* 2002;17:267–77.
- [21] Isaacssohn JL, Moser M, Stein EA, Dudley K, Davey K, Liskov E, et al. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. *Arch Int Med* 1998;158:1189–94.
- [22] Murphy LS, Reinsch S, Najm WI, Dickerson VM, Seffinger MA, Adams A, et al. Searching biomedical databases on complementary medicine: the use of controlled vocabulary among authors, indexers and investigators. *BMC Complement Altern Med* 2003;3:3.
- [23] McGregor B. Medical indexing outside the National Library of Medicine. *J Me Libr Assoc* 2002;90:339–41.
- [24] Kronenberg F, Molholt P, Zeng ML, Eskinazi D. A comprehensive information resource on traditional, complementary, and alternative medicine: toward an international collaboration. *J Altern Complement Med* 2001;7:723–9.
- [25] Pietri S, Seguin JR, d'Arbigny P, Drieu K, Culcasi M. Ginkgo biloba extract (EGb 761) pretreatment limits free radical-induced oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc Drugs Ther* 1997;11:121–31.
- [26] Savulescu J, Chalmer I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *BMJ* 1996;313:1390–3.
- [27] Ho FM, Hunag PJ, Lee FK, Chern TS, Chiu TW, Liao CS. Effect of acupuncture at Nei-Kuan on left ventricular function in patients with coronary artery disease. *Am J Chin Med* 1999;27:149–56.
- [28] Xueping Z, Zhongying Z, Miaoewen J, Hong W, Mianhua W, Yaohong S, et al. Clinical study of Qingluo Tongbi Granules in treating 63 patients with rheumatoid arthritis of the type yin-deficiency and heat in the collaterals. *J Trad Chin Med* 2004;24(2):83–7.
- [29] Johnson ES. *Feverfew: a traditional remedy for migraine and arthritis*. London: Sheldon Press; 1984.
- [30] Shelton RC, Keller MB, Gellenberg A, Dunner DL, Hirschfeld R, Thase ME, et al. Effectiveness of St. John's wort in major depression: a randomized controlled trial. *JAMA* 2001;285:1978–86.
- [31] Roberts C. The implications of variation in outcome between health professionals for the design and analysis of randomized controlled trials. *Stat Med* 1999;18:2605–15.
- [32] Dreikorn K, Borkowski A, Braeckman J, Denis L, Ferrari P, Gerber G, et al. Other medical therapies. In: Denis L, Griffiths K, Khoury S, Cockett ATK, McConnell J, Chatelain C, Murphy G, Yoshida O, editors. *Proceedings of the 4th international consultation on benign prostatic hyperplasia (BPH)*. Plymouth: Plymbridge Distributors; 1998. p. 633–59.
- [33] Dreikorn K, Lowe F, Borkowski A, Buck C, Braeckman J, Chopin D. Other medical therapies. In: Chatelain, Denis L, Foo KT, Khoury S, McConnell J, editors. *Proceedings of the 5th international consultation on benign prostatic hyperplasia (BPH)*. Plymouth: Plymbridge Distributors; 2001. p. 479–511.
- [34] Harkey MR, Henderson GL, Gershwin ME, Stern JS, Hackman RM. Variability in commercial Ginseng products: an analysis of 25 preparations. *Am J Clin Nutr* 2002;75:600–1.
- [35] Gurley BJ, Gardner SF, Hubbard MA. Content versus label claims in ephedra-containing dietary supplements. *Am J Health Syst Pharm* 2000;57:963–9.

- [36] Liberti LE, Der Marderosian A. Evaluation of commercial ginseng products. *J Pharm Sci* 1978;67:1487–9.
- [37] Groenewegen WA, Heptinstall S. Amounts of feverfew in commercial preparations of the herb. *Lancet* 1986;1:44–5.
- [38] Heptinstall S, Awang DV, Dawson BA, Kindack D, Knight DW, May J, et al. Parthenolide content and bioactivity of feverfew (*Tanacetum parthenium* [L.] Schultz-Bip.). Estimation of commercial and authenticated feverfew products. *J Pharm Pharmacol* 1992;44:391–5.
- [39] Nelson MH, Cobb SE, Shelton J. Variations in parthenolide content and daily dose of feverfew products. *Am J Health Syst Pharm* 2002;59:1527–31.
- [40] Zhang H, Yu C, Jia JY, Leung SW, Siow YL, Man RY, et al. Contents of four active components in different commercial crude drugs and preparations of danshen (*Salvia miltiorrhiza*). *Acta Pharmacol Sin* 2002;23:1163–8.
- [41] Manning J, Roberts JC. Analysis of catechin content of commercial green tea products. *J Herb Pharmacother* 2003;3(3):19–32.
- [42] Schulte-Lobbert S, Holloubek G, Muller WE, Schubert-Zsilavecz M, Wurglics M. Comparison of the synaptosomal uptake inhibition of serotonin by St. John's wort products. *J Pharm Pharmacol* 2004;56:813–8.
- [43] Garrara J, Hamrs S, Eberly LE, Matiak A. Variations in product choices of frequently purchased herbs: caveat emptor. *Arch Int Med* 2003;163:2290–5.
- [44] Weber HA, MK Zart, Hodges AE, Molloy HM, O'Brien BM, Moody LA, et al. Chemical comparison of goldenseal (*Hydrastis canadensis* L.) root powder from three commercial suppliers. *J Agric Food Chem* 2003;51:7352–8.
- [45] Carlson M, Thompson RD. Liquid chromatographic determination of methylxanthines and catechins in herbal preparations containing guarana. *J AOAC Int* 1998;81:691–701.
- [46] Lefebvre T, Foster BC, Drouin CE, Krantis A, Livesy JF, Jordan SA. In vitro activity of commercial valerian root extracts against human cytochrome P450 3A4. *J Pharm Pharm Sci* 2004;7:265–73.
- [47] Oberlies NH, Kim NC, Brine DR, Collins BJ, Handy RW, Sparacino CM, et al. Analysis of herbal teas made from the leaves of comfrey (*Symphytum officinale*): reduction of N-oxides results in order of magnitude increases in the measurable concentration of pyrrolizidine alkaloids. *Public Health Nutr* 2004;7:919–24.
- [48] Haller CA, Duan M, Benowitz NI, Jacob P. Concentrations of Ephedra alkaloids and caffeine in commercial dietary supplements. *J Anal Toxicol* 2004;28:145–51.
- [49] Sevenpiper JL, Arnason JT, Leiter LA, Vuksan V. Variable effects of American ginseng: a batch of American ginseng (*Panax quinquefolius* L.) with a depressed ginsenoside profile does not affect postprandial glycemia. *Eur J Clin Nutr* 2003;57:243–8.
- [50] Greuter W, McNeill J, Barrie FR, Burdet HM, Demoulin V, Figueiras TS, et al. International Code of Botanical Nomenclature (ST LOUIS CODE), adopted by the Sixteenth International Botanical Congress, St Louis, Missouri, July 1999. Available at <http://www.bgbm.fu-berlin.de/iapt/nomenclature/code/SaintLouis/0000St.Luistitle.htm> (Accessed July 2004).
- [51] Pellati F, Benvenuti S, Margro L, Melegari M, Soragni F. Analysis of phenolic compounds and radical scavenging activity of *Echinacea* spp. *J Pharm Biomed Anal* 2004;35:289–301.
- [52] Vuksan V, Sevenpiper JL, Wong J, Xu Z, Beljan-Zdravkovic U, Arnason JT, et al. American ginseng (*Panax quinquefolius* L.) attenuates postprandial glycemia in a time-dependent but not dose dependent manner in healthy individuals. *Am J Clin Nutr* 2001;73:753–8.
- [53] Morgenstern C, Biermann E. The efficacy of Ginkgo special extract Egb 761 in patients with tinnitus. *Int J Clin Pharmacol Ther* 2003;5:188–97.
- [54] Betz JM, Eppley RM, Taylor WC, Andrzejewski D. Determination of pyrrolizidine alkaloids in commercial comfrey products (*Symphytum* sp.). *J Pharm Sci* 1994;83:649–53.
- [55] Patora J, Majda T, Gora J, Klimek B. Variability in the content and composition of essential oil from lemon balm (*Melissa officinalis* L.) cultivated in Poland. *Acta Pol Pharm* 2003;60(5):395–400.
- [56] Drew S, Davies E. Effectiveness of *Ginkgo biloba* in treating tinnitus: double blind, placebo controlled trial. *BMJ* 2001;322:1–6.
- [57] Vuksan V, Starva MP, Sevenpiper JL, Koo VYY, Wong E, Beljan-Zdravkovic U, et al. American Ginseng improves glycemia in individuals with normal glucose tolerance: effect of dose and time escalation. *J Am Coll Nutr* 2000;19:738–44.
- [58] Swanson CA. Suggested guidelines for articles about botanical dietary supplements. *Am J Clin Nutr* 2002;75:8–10.
- [59] Instructions to authors. *Phytomed Int J Phytother Phytopharmacol*. Available at http://www.elsevier.de/artikel/805109&_text=&_text=autorehinweise (accessed July 2004).
- [60] German Federal Institute for Drugs and Medical Device. The complete German Commission E monographs: therapeutic guide to herbal medicines. Boston, MA: Integrative Medicine Communications; 1999.
- [61] Bauer R, Tittel G. Quality assessment of herbal preparations as a precondition of pharmacological and clinical studies. *Phytomedicine* 2000;26:2(3):193–8.
- [62] Association of Analytical Communities (AOAC). Accessed Nov 1, 2004. Available at <http://www.aoac.org/>.
- [63] American Herbal Pharmacopoeia. Accessed Nov 1, 2004. Available at http://www.herbal-ahp.org/order_online.htm.
- [64] United States Pharmacopoeia. Accessed Nov 3, 2004. Available at http://www.uspverified.org/resource/requestform_man.html.
- [65] Chan K. Some aspects of toxic contaminants in herbal medicines. *Chemosphere* 2003;52:1361–71.
- [66] Murphy JJ, Heptinstall S, Mitchell JRA. Randomized double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet* 1988;2(8604):189–92.
- [67] Vickers AJ, de Craen AJM. Why use placebos in clinical trials? A narrative review of the methodological literature. *J Clin Epidemiol* 2000;53:157–61.
- [68] Palevitch D, Earon G, Carasso R. Feverfew (*Tanacetum parthenium*) as a prophylactic treatment for migraine: a double-blind placebo-controlled study. *Phytother Res* 1997;11:508–11.
- [69] Brinkhaus B, Hummelsberger J, Kohnen R, Seufert J, Hempen CH, Leonhardy H, et al. Acupuncture and Chinese herbal medicine in the treatment of patients with seasonal allergic rhinitis: a randomized-controlled clinical trial. *Allergy* 2004;59:953–60.
- [70] Bent S, Xu L, Lui L, Nevitt M, Schneider E, Tian G, et al. A randomized controlled trial of a Chinese herbal remedy to increase energy, memory, sexual function and quality of life in elderly adults in Beijing, China. *Am J Med* 2003;115:441–7.
- [71] Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. *BMJ* 1985;291:569–73.
- [72] Piscitelli SC, Burstein AH. Herb-drug interactions and confounding in clinical trials. *J Herb Pharmacother* 2002;2:23–6.
- [73] Pietri S, Seguin JR, d'Arbigny P, Drieu K, Culcasi M. Ginkgo biloba extract (EGB 761) pretreatment limits free radical-induced oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc Drugs Ther* 1997;11:121–31.
- [74] Dowling EA, Redondo DR, Branch JD, Jones S, McNabb G, Williams MH. Effect of *Eleutherococcus senticosus* on submaximal and maximal exercise performance. *Med Sci Sports Exerc* 1996;28:482–9.
- [75] Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology: the essentials. Philadelphia, PA: Lippincott; 1996.
- [76] Gardner CD, Chatterjee LM, Carlson JJ. The effect of a garlic preparation on plasma lipid levels in moderately hypercholesterolemic adults. *Atherosclerosis* 2001;154:213–20.
- [77] *Annals of Internal Medicine*. Information for authors. Accessed January 10, 2001. Available at <http://www.annals.org/>.