Reporting Random Controlled Trials of Herbal Medicines

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Background: Given that herbal medicinal products are widely used, vary greatly in content and quality, and are actively tested in randomized controlled trials (RCTs), such RCTs must clearly report the specifics of the intervention.

Objective: Our objective was to develop recommendations for reporting RCTs of herbal medicine interventions.

Methods: We identified and invited potential participants with expertise in clinical trial methodology, clinical trial reporting, pharmacognosy, herbal medicinal products, medical statistics, and/or herbal product manufacturing to participate in phone calls and a consensus meeting. Three phases were conducted: (1) Premeeting item generation via telephone calls, (2) Consensus meeting, and (3) Postmeeting feedback. Sixteen experts participated in premeeting phone calls for item generation, and 14 participants attended a consensus meeting in Toronto, Ontario, Canada, in June of 2004. During the consensus meeting, a modified Delphi technique was used to aid discussion and debate of information required for reporting RCTs of herbal medicines.

Results: After extensive discussion, the group decided that context-specific elaborations of nine Consolidated Standards of Reporting Trials (CONSORT) items to RCTs of herbal medicines were necessary: Item 1 (Title and Abstract), 2 (Background), 3 (Participants), 4 (Interventions), 6 (Outcomes), 15 (Baseline data), 20 (Interpretation), 21 (Generalizability), and 22 (Overall evidence).

Discussion: The elaboration of item 4 of the CONSORT statement outlines specific information required for complete reporting of the herbal medicine intervention. The reporting suggestions presented will support clinical trialists, editors, and reviewers in reporting and reviewing RCTs of herbal medicines and readers in interpreting the results.

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BACKGROUND

Randomized controlled trials (RCTs) provide the best evidence for efficacy of healthcare interventions.[1] Low-quality reports of RCTs, compared with higher quality ones, exaggerate the estimates of a treatment's effectiveness (for example, see Schulz et al[2]). Hence, efforts have been made to improve the quality of reporting.[3,4]

The Consolidated Standards of Reporting Trials (CONSORT) statement was first published in 1996 and revised in 2001.[3,4] This statement comprises a 22-item checklist and flow diagram to guide authors, peer reviewers, editors, and readers on the essential information required in reports of two-group parallel RCTs.[3,4] The CONSORT statement is endorsed by leading medical journals, editorial groups, professional societies, and funding bodies.[5] Since its inception, several extensions and context-specific applications of the CONSORT statement have been developed (for example, see Campbell et al[6] and Ioannidis et al[7]). This paper describes the application of the CONSORT checklist to RCTs of herbal medicinal (See Appendix B) products.

Reports of controlled trials of herbal medicines must clearly document all aspects of implementation, analysis, results, and interpretation as recommended in the CONSORT statement. Several studies suggest that reports of complementary and alternative medicine (CAM) RCTs inadequately describe important aspects of their methodology.[8–12] For example, a sample of pediatric CAM RCTs reported less than 40% of all necessary information outlined in the CONSORT checklist.[10] By comparison, RCTs of conventional medicine interventions have been found to report between 40% and 60% of the information outlined in the CONSORT checklist.[13,14] More specifically, one study showed that only 50% of CAM trials reported how random numbers were generated and 25% if allocation conceal-

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ment was done.[9] In herbal medicine trials, only 28% of the reports described whether the person administering the intervention was blinded to group assignment or not, only 22% described the methods for implementing the allocation sequence, and just 21% described the method for generating the allocation sequence.[11] Although the reporting quality of herbal medicine trials appears to be improving, these trial reports are still missing important information. Of particular importance is the reporting of the herbal intervention.

Crude herbal drugs are natural products, and their chemical composition, therefore, varies, depending on several factors, such as geographical source of the plant material, climate in which it was grown, time of harvest, and so on. It follows that commercially available herbal medicinal products also vary in their content and concentration of chemical constituents from batch-to-batch and, when different products containing the same herbal ingredient are compared, from manufacturer-to-manufacturer.[15–22] Even in instances in which herbal products are standardized for content of known active or marker compounds to achieve more consistent pharmaceutical quality, there is variation in the concentrations of other constituents. Furthermore, the true chemical content of some commercially available herbal products is different to that stated on their labels.[20,23,24] These variations can result in differences in pharmacological activity in vitro[25] and in bioavailability in man,[26] which is of clinical relevance. Quantitative and qualitative variations in the content of herbal medicinal products are not limited to active or otherwise desirable constituents; variation in concentrations of toxic constituents has also been reported.[27] For these reasons, it should not be assumed that the results of an RCT of a particular herbal intervention (eg, an extract of *Ginkgo biloba* leaf standardized to contain 24% ginkgo flavone glycosides) can be generalized to all products containing or made from the same herb (eg, all *Ginkgo biloba* products). Therefore, it is imperative that reports of RCTs of herbal medicine interventions provide clear and complete descriptions of the intervention.[28,29]

Against this background, our objective was to develop reporting recommendations for RCTs of herbal medicine interventions by elaborating on the 22-item checklist of the CONSORT statement to guide authors, peer reviewers, and editors on appropriate reporting for such studies. Here, we present recommendations regarding the checklist items for herbal interventions; further explanations and examples of good reporting will be published separately.

METHODS

The process used to develop the reporting recommendations for RCTs of herbal medicines interventions consisted of three phases: (1) Premeeting item generation, (2) Consensus meeting, and (3) Postmeeting feedback. We identified and invited potential participants based on their international reputations and peer-reviewed publications with expertise in clinical trial methodology and/or reporting (n = 5), pharmacognosy (n = 4), herbal medicinal products (n = 5), medical statistics (n = 1), and herbal product manufacturing (n = 1). Individuals who agreed to participate were mailed a selection of articles on herbal medicine interventions and reporting quality. During May and June of 2004, 16 participants were contacted by telephone by one investigator (J.G.) and asked to suggest necessary revisions to existing CONSORT items and additional/new items required for reporting herbal medicine RCTs. Participants were asked to consider items based on empirical evidence that not reporting them would bias the estimates of treatment effect. In instances in which no empirical evidence was available, common sense reasoning was acceptable. When all phone calls were completed, one individual (J.G.) thematically grouped items and circulated them for review by each participant.

The second phase, took place in Toronto, Ontario, Canada, on June 28th and 29th, 2004, and was attended by 14 individuals from various countries including Canada (n = 7), England (n = 3), United States (n = 2), India (n = 1), and Germany (n = 1). In addition, two research assistants, the meeting coordinator (J.G.) and meeting chair (C.B.) attended. The meeting began with a review of the premeeting item suggestions generated from the phone calls. The meeting coordinator and chair emphasized the need to keep item extensions and additions to a minimum and that they be based on evidence if possible. Participants agreed that, rather than adding items to the existing CONSORT checklist, several items required context-specific elaborations for relevance to herbal medicine interventions.

We refined the suggestions using a modified Delphi technique.[30] Specifically, item suggestions were presented and followed by debate and presentation of empirical evidence or common sense reasoning for or against each. These were modified and deleted based on these discussions and group consensus. The meeting took place over an evening session, followed by a full-day meeting of the assembled group. Within eight weeks of the consensus meeting, a draft report was circulated to all participants to ensure that the report accurately represented the decisions made during the consensus meeting. The manuscript was then circulated to the wider CONSORT Group for their input. The report was revised in light of these suggestions.

RESULTS

Rather than adding new items to the CONSORT statement, the group decided that nine existing CONSORT items needed elaboration for relevance to RCTs of herbal medicine intervention. The recommendations are listed in Tables 1 and 2 and are intended to be used in conjunction with the 22 existing CONSORT items. In Table 1, CONSORT items appear in normal text and recommendations for reporting RCTs of herbal medicine in italicized text. Table 2 contains a detailed outline of recommendations for reporting the herbal medicine intervention, an elaboration on CONSORT item 4.

CONSORT items requiring specific elaboration for relevance to RCTs of herbal medicine interventions were (see Tables 1 and 2) as follows: Item 1 (Title and Abstract), 2 (Background), 3 (participants), 4 (interventions), 6 (Outcomes), 15 (Baseline data), 20 (Interpretation), 21 (Generalizability), and 22 (Overall evidence).

The title and/or abstract (Item 1) should include the Latin binomial for the plant species from which the herbal medicine(s) originated, the part(s) of the plant used in the preparation, and

Table 1. Proposed Elaborations of CONSORT Items for Randomized Controlled Trials of Herbal Medicine Interventions[a]

Standard CONSORT Checklist: Paper Section and Topic	Standard CONSORT Checklist: Item	Descriptor	Reported on Page Number
Title and abstract	1	How participants were allocated to interventions (eg, "random allocation," "Randomized" or "randomly assigned"). 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.	
Introduction		Scientific background and explanation of the rationale.	
Background	2	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.	
Methods		Eligibility criteria for participants and the settings and locations where the data were collected.	
Participants	3	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.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered. A detailed description of this item appears in table 2.	
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 (eg, multiple observations, training of assessors). Outcome measures should reflect the intervention and indications tested, considering, where applicable, underlying theories and concepts.	
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 (eg, blocking, stratification).	
Allocation concealment	9	Method used to implement the random allocation sequence(eg, 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.	
Results Participant flow	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.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group. Including concomitant medication, herbal and complementary medicine use.	
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 (eg, 10/20, not 50%).	

Table 1. Continued

Standard CONSORT Checklist: Paper Section and Topic	Standard CONSORT Checklist: Item	Descriptor	Reported on Page Number
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 (eg, 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.	
Discussion 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. *Interpretation of the results in light of the product and dosage regimen used.*	
Generalizability	21	Generalizability (external validity) of trial results. Where possible, discuss how the herbal product and dosage regimen used relate to what is used in self-care and/or practice.	
Overall evidence	22	General interpretation of the results in the context of current evidence. Discussion of the trial results in relation to trials of other available products.	

[a]CONSORT items (1, 12) are listed in normal text. Proposed implementations for relevance to reports of herbal medicine RCTs are list in italicized text.

the type of preparation (eg, dried crude herb, ethanolic extract). The background (Item 2) should include a statement explaining the rationale for investigation of the specific herbal medicinal product and whether the indication for which it is being tested is new or is based on traditional use. Participant eligibility criteria (item 3) in a trial testing a traditional indication (eg, in traditional Chinese herbal medicine, a trial may test the effects of a herbal medicine intervention for liver chi (Qi) deficiency) should describe the theories and concepts underlying this indication.

The description of the intervention (item 4;)Table 2 must include the herbal medicinal product name, manufacturer, plant part used, type of preparation, source and authentication of the herbal material, pharmaceutical quality (eg, herbal drug-to-extract ratio, type and concentration of the extraction solvent, quantity of active constituents per unit dose), dosage regimen, and qualitative testing (purity). Also, reporting of the rationale for the control/placebo used in the trial is recommended. For studies involving herbal medicine, practitioners as part of the intervention, details of practitioners (eg, training, registration status) should be reported. Not all recommendations are relevant for all types herbal medicine interventions. Therefore, we begin this section with the words "*where applicable*." For example, a report of an RCT of an herbal medicinal product comprising crude herbal material (eg, leaves, stems, root) prepared as a tea or decoction does not require reporting of the "*type and concentration of solvent used and the plant to plant extract ratio*" (Table 2.B.3.). In addition, herbal interventions made by the investigators specifically for the study will not have a finished product or extract name or manufacturer (Table 2.A.2.). For such products, all methods used in preparing and formulating the product must be reported. Similarly, in Table 2, item 4.F. is only relevant for studies in which the practitioner is a part of the intervention. In other studies, the practitioner may serve a more neutral role, and, thus, their characteristics need not be reported. With these exceptions, all information outlined in these recommendations is suggested to be reported for all herbal medicine interventions.

Also, outcome measures (item 6) should reflect the intervention and indications tested while considering their underlying theories and concepts. For the results section, it is recommended that, in addition to other baseline data (item 15), RCTs of herbal medicine interventions report any concomitant medication, herbal medicinal product, or other CAM use. It is recommended that, when interpreting the results (item 20), there be consideration of the specific herbal product and dosage regimen tested. This includes an overview of evidence on this particular herbal medicinal product. When considering generalizability (item 21), it is suggested that authors report how the product used in the trial generalizes to products used in self-care and/or in clinical practice. Finally, when interpreting the results in the context of the evidence (item 22), it is recommended that a general discussion in relation to trials of other available products should be reported.

DISCUSSION

The CONSORT statement outlines information required in reports of any two-group parallel RCT design.[1] We have developed and described recommendations (See Tables 1 and 2) to be used in conjunction with the existing CONSORT checklist when reporting RCTs of herbal medicine interventions. These recommendations were developed to guide clinical trialists, editors, and reviewers in reporting and reviewing RCTs of herbal medicine interventions. Beyond RCTs, these recommendations are relevant for the reporting of herbal interventions in other

Table 2. Proposed Elaboration of CONSORT Item 4 for Reporting Randomized Controlled Trials of Herbal Medicine Interventions

Standard CONSORT Checklist: Paper Section and Topic	Standard CONSORT Checklist: Item	Descriptor	Reported on Page Number
Methods	4.	Where applicable, the description of a herbal intervention should include:	
Interventions	4.A.Herbal medicinal product name	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 (ie, brand name) or the extract name (eg, 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	1. The part(s) of plant used to produce the product or extract. 2. The type of product used (eg, raw [fresh or dry], extract) 3. The type and concentration of extraction solvent used (eg, 80% ethanol, H_2O 100%, 90% glycerine, and others) and the herbal drug to extract ratio (drug: extract; eg, 2:1) 4. The method of authentication of raw material (ie, how done and by whom) and the lot number of the raw material. State whether a voucher specimen (ie, retention sample) was retained and, if so, where it is kept or deposited and the reference number	
	4.C. Dosage regimen and quantitative description	1. The dosage of the product, the duration of administration, and how these were determined 2. The content (eg, 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; eg, 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	1. Product's chemical fingerprint and methods used (equipment and chemical reference standards) and who performed it (eg, the name of the laboratory used). Whether or not a sample of the product (ie, retention sample) was retained and, if so, where it is kept or deposited 2. Description of any special testing/purity testing (eg, heavy metal or other contaminant testing) undertaken. Which unwanted components were removed and how (ie, methods) 3. Standardization: what to (eg, which chemical component(s) of the product) and how (eg, chemical processes or biological/functional measures of activity)	
	4.E. Placebo/control group	The rationale for the type of control/placebo used	
	4.F. Practitioner	A description of the practitioners (eg, training and practice experience) who are a part of the intervention	

research designs, whether preclinical (eg, in vivo, in vitro) or clinical (eg, number of participants of 1 trial).

The type of information 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] For controlled trials of herbal medicines, the information recommended when reporting the herbal intervention (item 4; Table 2) is essential to provide a complete description of the herbal product being tested. There is a wide variety of commercially available products containing herbal medicines. Unfortunately, there is great variability in the content of these products.[15–24] Products may not contain the amount (weight, volume, proportion) of individual constituents listed on their labels[19] or any of the constituents at all. Also, products containing the same botanical species often contain varying amounts of the plant's marker/active constituents (see Appendix B) (for example, see Manning and Roberts[19] and Carlson and Thompson[20]). A thorough description of the product will allow for the valid and reliable determination of efficacy and safety of specific herbal products.

Since publication of the CONSORT statement, data suggest that there has been a significant increase in the quality of reports of RCTs in journals that endorse it, recognizing that this might not translate into journal adherence.[14,31] In an effort to evaluate the impact of the recommendations for reporting herbal medicine interventions, we plan to evaluate their influence on the reporting of herbal medicine RCTs. To support this initiative, we invite journal editors to include a reference to these recommendations[32] or a copy of the checklist (www.annals.org.) in their journal's instructions to authors because this will likely support the improvement of reporting of RCTs of herbal medicine interventions.

In an effort to keep the checklist evidence based, incorporate emerging data, and up-to-date, we will periodically update the recommendations. The goal being improved reporting, which ultimately will support clear interpretation of trial methods and results, improving the validity of inferences derived from trial findings.[33]

In addition to this overview, an explanatory document has been produced that describes each recommendation in detail and provides examples of good reporting and empirical evidence for individual items where available.[34]

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Joel Gagnier conceptualized the study design, identified and secured funding, identified and invited participants, coordinated the consensus meeting and phone calls, wrote, edited and revised the manuscript. Heather Boon conceptualized the study design, identified and secured funding, identified and invited participants, edited and commented upon the manuscript. Paula Rochon conceptualized the study design, identified and secured funding, edited and commented upon the manuscript. David Moher conceptualized the study design, identified and invited participants, edited and commented upon the manuscript. Joanne Barnes edited and commented upon the manuscript. Claire Bombardier conceptualized the study design, identified and secured funding, identified and invited participants and, edited and commented upon the manuscript.

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APPENDIX A.
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 items.

Doug Altman (Cancer Research UK Medical Statistics Group, Centre for Statistics in Medicine, Oxford, United Kingdom); Joanne Barnes (Centre for Pharmacognosy and Phytotherapy, The School of Pharmacy, University of London, London, United Kingdom); 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); 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); 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, United Kingdom); David Riley (University of New Mexico Medical School, Santa Fe, NM); 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).

The members of the CONSORT Group are listed on the following Web site: http://www.consort-statement.org/profiles/partners.html.

APPENDIX B.
Terms

Herbal medicine: The term herbal medicine and herbal medicinal product will be used synonymously throughout this manuscript. 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.)

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 a group or groups of constituents. A marker compound, or group of marker compounds, is a plant constituent used as a proxy measurement tool for the full spectrum of compounds in the botanical product and is selected because it is characteristic for that plant/plant part, for example, because it is present in a substantial concentration. This is typically, but not always, a single compound.