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