Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials

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Summary

Background Erythropoiesis-stimulating agents reduce anaemia in patients with cancer and could improve their quality of life, but these drugs might increase mortality. We therefore did a meta-analysis of randomised controlled trials in which these drugs plus red blood cell transfusions were compared with transfusion alone for prophylaxis or treatment of anaemia in patients with cancer.

Methods Data for patients treated with epoetin alfa, epoetin beta, or darbepoetin alfa were obtained and analysed by independent statisticians using fixed-effects and random-effects meta-analysis. Analyses were by intention to treat. Primary endpoints were mortality during the active study period and overall survival during the longest available follow-up, irrespective of anticancer treatment, and in patients given chemotherapy. Tests for interactions were used to identify differences in effects of erythropoiesis-stimulating agents on mortality across prespecified subgroups.

Findings Data from a total of 13 933 patients with cancer in 53 trials were analysed. 1530 patients died during the active study period and 4993 overall. Erythropoiesis-stimulating agents increased mortality during the active study period (combined hazard ratio [cHR] 1.17, 95% CI 1.06–1.30) and worsened overall survival (1.06, 1.00–1.12), with little heterogeneity between trials (I² 0%, p=0.87 for mortality during the active study period, and I² 7%, p=0.33 for overall survival). 10 441 patients on chemotherapy were enrolled in 38 trials. The cHR for mortality during the active study period was 1.10 (0.98–1.24), and 1.04 (0.97–1.11) for overall survival. There was little evidence for a difference between trials of patients given different anticancer treatments (p for interaction=0.42).

Interpretation Treatment with erythropoiesis-stimulating agents in patients with cancer increased mortality during active study periods and worsened overall survival. The increased risk of death associated with treatment with these drugs should be balanced against their benefits.

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Introduction Erythropoiesis-stimulating agents increase haemoglobin concentrations, reduce the need for red blood cell transfusions, and could improve quality of life in patients with cancer. However, they have been reported to increase the risk of thromboembolic events and might stimulate tumour growth. Uncertainty remains about whether and how these drugs affect survival; their safety has been discussed repeatedly at hearings of the US Food and Drug Administration and the European Medicines Agency.

Previous studies addressing this issue were literature-based meta-analyses of aggregated results that combined heterogeneous mortality endpoints and could not examine whether effects differed across subgroups—eg, patients with different haemoglobin concentrations at baseline. These limitations can be overcome in meta-analyses that are based on individual patient data, but up till now such meta-analyses have been small (2301 and 2112 patients), focused on epoetin beta or darbepoetin alfa, and were sponsored by the manufacturers. Since erythropoiesis-stimulating drugs are widely used in patients with cancer, more definitive analyses of mortality in individuals randomly assigned to receive or not to receive these drugs are needed.

We therefore did a comprehensive meta-analysis that was based on the individual patient data from randomised controlled trials, including trials done by manufacturers of erythropoiesis-stimulating agents and independent investigators. Our objectives were to examine the effects of these drugs on the survival of patients with cancer and to identify factors that might modify such effects.

Methods Patients and study selection Main analyses were defined in a peer-reviewed protocol and a statistical analysis plan, and main analyses were done independently in two academic departments. A steering committee consisting of clinicians and methodologists reviewed results and agreed on their interpretation.
In eligible studies, erthropoiesis-stimulating agents were compared with placebo or with standard care. We defined mortality during the active study period as death from any cause between date of randomisation and 28 days after the end of the active study phase, and overall survival as death from any cause between date of randomisation and date of the last available follow-up. We classified studies according to cancer treatments (chemotherapy, radiotherapy, radiochemistry, no treatment, or other). At least 70% of patients had to be given the planned anticancer treatment. Trials or trial strata were excluded if more than 20% of patients had an ineligible condition. Studies with planned sample sizes fewer than 100 patients or analyses based on fewer than 50 patients were also excluded.

We searched Medline, Embase, Cochrane Library, and conference proceedings, from Jan 1, 1985, to Jan 31, 2008, for eligible trials (for the detailed search strategy see Bohlius and colleagues15). Searches were supplemented with studies identified by manufacturers of erthropoiesis-stimulating agents. Two reviewers (JB, OW) independently assessed studies for eligibility, and discrepancies were resolved by consensus.

Manufacturers and triallists provided individual patient data and study variables in a standardised format. All data were anonymised, encrypted, and sent to the data centre at the University of Cologne, Cologne, Germany, where data were checked for accuracy, consistency, plausibility, and completeness of follow-up. Two reviewers (JB, SK) independently extracted additional study data from reports, study protocols, and clinical study reports.

### Outcomes, definitions, and study quality

The primary outcomes were mortality during the active study period and overall survival in all patients and in those on chemotherapy. We defined mortality during the active study period as death from any cause between date of randomisation and 28 days after the end of the active study phase, and overall survival as death from any cause between date of randomisation and date of the last available follow-up. We classified studies according to cancer treatments (chemotherapy, radiotherapy, radiochemistry, no treatment, or other). At least 70% of patients had to be given the planned anticancer treatment to qualify for a particular category. The quality of studies was assessed independently by JB and SK using study protocols, clinical study reports, publications, and additional information from investigators. The components examined included generation of randomisation sequence (adequate vs unclear), concealment of allocation (adequate vs unclear), blinding (double-blind, placebo-controlled vs other), type of mortality endpoint (primary vs secondary endpoint vs adverse event), planned long-term follow-up (yes vs no), use of standardised chemotherapy or radiotherapy treatment protocol (yes vs no), and termination of study earlier than planned (yes vs no).

### Statistical analysis

For each trial, we examined differences in baseline characteristics and follow-up times between patients given erthropoiesis-stimulating agents and those in the control groups, and assessed the proportional hazard assumption. Both one-stage and two-stage meta-analytic methods were used to analyse individual patient data.6,36 We calculated log hazard ratios with log-rank test and Cox regression for each study and combined these in fixed-effects and random-effects meta-analyses (two-stage method). We also calculated Cox regression models stratified by study (one-stage fixed-effects method). Trials with no events in both groups did not contribute to meta-analyses. All analyses were by intention to treat. In the two-stage method, between trial heterogeneity was assessed by the $I^2$ statistic, and funnel plot asymmetry was assessed with linear regression.27,28 We assessed the effect of individual studies on combined estimates.

### Figure 1: Identification of eligible trials

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We adjusted for baseline imbalances of prognostic factors in stratified Cox models (one-stage method). Patients were excluded from analyses if data for variables included in the model were missing. Variables with a p value from the likelihood-ratio test of less than 0.10 were included in multivariate models. Potential effect modifiers were examined in models that included an additional variable besides the treatment factor. Variables in these models were age; sex; baseline concentrations of ESA; Control; Total 7634 (55%) 6299 (45%)

Haemoglobin concentration (g/L)
- ≤80: 448 (6%) 343 (5%)
- >80 to ≤100: 2222 (29%) 1708 (27%)
- >100 to ≤120: 2851 (37%) 2153 (34%)
- >120 to ≤140: 1433 (19%) 1410 (22%)
- >140: 428 (6%) 411 (7%)
- Missing/not reported: 252 (3%) 274 (4%)

Tumour type
- Haematological: 1400 (18%) 1003 (16%)
- Breast: 2245 (29%) 2057 (33%)
- Head and neck: 443 (6%) 425 (7%)
- Lung: 1618 (21%) 1458 (23%)
- Gastrointestinal: 434 (6%) 274 (4%)
- Gynaecological: 842 (11%) 557 (9%)
- Genitourinary: 266 (3%) 176 (3%)
- Other: 369 (5%) 324 (5%)
- Missing/not reported: 17 (<1%) 25 (<1%)

Tumour stage
- Metastatic/advanced: 4482 (59%) 3631 (58%)
- Not metastatic or advanced: 2116 (28%) 1923 (31%)
- Unclear, missing, not reported: 1036 (14%) 745 (12%)

Sex
- Men: 2854 (37%) 2282 (36%)
- Women: 4780 (63%) 4017 (64%)

Age (years) at randomisation
- <18: 55 (<1%) 68 (1%)
- ≥18 to <35: 191 (3%) 155 (2%)
- ≥35 to <45: 745 (10%) 675 (10%)
- ≥45 to <55: 1614 (21%) 1396 (22%)
- ≥55 to <65: 2237 (29%) 1956 (31%)
- ≥65 to <75: 1970 (26%) 1547 (25%)
- ≥75: 816 (11%) 573 (9%)
- Missing/not reported: 17 (<1%) 25 (<1%)

Haematocrit baseline categories
- ≤0.235: 210 (3%) 180 (3%)
- >0.235 to ≤0.294: 1567 (21%) 1221 (19%)
- >0.294 to ≤0.353: 2962 (35%) 1923 (31%)
- >0.353 to ≤0.412: 1258 (16%) 1200 (19%)
- >0.412: 414 (5%) 371 (6%)
- Missing/not reported: 1493 (20%) 1404 (22%)

Baseline serum erythropoietin (IU/L)
- <25: 876 (11%) 621 (10%)
- ≥25 to <100: 1643 (22%) 1265 (20%)
- ≥100 to <200: 451 (6%) 289 (5%)
- ≥200 to <500: 190 (2%) 135 (2%)
- ≥500: 103 (1%) 78 (1%)
- Missing/not reported: 4371 (57%) 3911 (62%)

(Continues in next column)
haemoglobin, haematocrit, and serum erythropoiesis-stimulating hormones; haemoglobin treatment upper limits; history of thromboembolism, cardiovascular events, diabetes, and arterial hypertension; type and stage of tumour; frequency of administration, duration of treat-
ment, and dose of erythropoiesis-stimulating agents; and components of study quality. We also did posthoc analyses stratified by the Food and Drug Administration licensing indications (on-label vs off-label). In sensitivity analyses of placebo-controlled trials, we excluded patients who had not been given the intervention they were assigned to (per-protocol analysis) and estimated the complieraveraged causal effect on mortality during the active study periods. Further details on these sensitivity analyses are provided in the webappendix (p 49).

Results are presented as hazard ratios (HRs) with 95% CIs for comparison of a erythropoiesis-stimulating agent with the control. We calculated numbers needed to treat for an additional death (NNTH).

Role of the funding source
Representatives of the manufacturers of erythropoiesis-stimulating agents contributed data and were members of the advisory board. Manufacturers and funding sources had no influence on the study design, analysis, and interpretation of data, writing of the report, and decision to submit the report for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
We identified 63 eligible studies and 53 (84%) contributed individual patient data (figure I). Three manufacturers of erythropoiesis-stimulating agents (Aagen, Johnson & Johnson, and Hoffmann-La Roche) and five independent investigators provided individual patient data. 1,2,15–21 14206 patients were included in the dataset; 273 (2%) were excluded for the following reasons: no study arm was allocated (n=164), they had leukaemia and were included in a separate stratum (n=98), 22 or date of randomisation was missing (n=11). A total of 13333 patients were included in the analyses (further details are provided in the webappendix p1).

Chemotherapy was given to patients in 38 (72%) of 53 studies included in the meta-analysis (Angermund R and Murphy R, Janssen-Cilag, personal communication), 2,15,16,21,22 radiotherapy in three (6%) 8,17,18 and radiochemotherapy in five (9%). 8,19,20,23,24 In a further five (9%) studies, no chemotherapy or radiotherapy was given to patients. 23,24,25 Two studies were assessed in the category called other since less than 70% of patients included had been given chemotherapy. 22,23 28 (53%) studies were placebo-controlled. Randomisation procedures were adequately reported in 16 (30%) studies, and the method of randomisation was unclear in the remaining 37 (70%). Survival was the primary endpoint in five (9%) studies, 22,23,21,22,25 and the secondary endpoint in 15 (28%) studies, and mortality was included as a safety or adverse outcome in 33 (62%) studies. Two (4%) studies were in

![Figure 2: Mortality in all patients with cancer during active study periods](See Online for webappendix)
progress at the time of analysis, 14 (26%) ended prematurely, and 37 (70%) were completed.23,24

The planned epoetin dose was from 21 000 IU to 26 117 IU per week; in 20 (38%) studies the duration of treatment with erythropoiesis-stimulating agents was equal to or greater than 150 g/L in two studies5,62 and equal to or greater than 4 months of the active study period in patients given erythropoiesis-stimulating agents was equal to or greater than 150 g/L in two studies6,58 and equal to or greater than 8 weeks to 52 weeks; in 20 (38%) studies the duration of treatment with erythropoiesis-stimulating agents was 8∙4 months (3∙7–19∙1) in the control arm. The combined HR was 1∙17 (95% CI 1∙08–1∙27; p = 0∙001; figure 2). Trial results were homogeneous (I² 0%, p = 0∙87) and the results with fixed-effects and random-effects models were identical.

Two studies24 contributed more than 10% weight to the overall analysis. Results were robust when we excluded one study at a time. In 38 chemotherapy trials, 5676 patients were randomly assigned to erythropoiesis-stimulating agents and 4765 to control. Median follow-up of patients in chemotherapy trials was 4·1 months (IQR 3·0–5·6) in the erythropoiesis-stimulating agent groups and 4·3 months (3·4–5·7) in the control groups. The combined HR was 1·10 (95% CI 0·98–1·24; p = 0·12; figure 3), with little evidence of heterogeneity between trials (I² 0%, p = 0∙72). One study25 contributed 20% weight to the overall analysis; exclusion of this study reduced the overall HR to 1·03 (0·90–1·18); and exclusion of other studies did not substantially affect the results. Similarly, results changed little when we excluded patients who had not been given chemotherapy in trials classified as chemotherapy trials.

In the assessment of overall patient survival, median follow-up of all patients was 6·2 months (IQR 3·2–15·4) in the erythropoiesis-stimulating agent arm and 8·3 months (3·7–19·6) in the control arm. The combined HR was 1·06 (95% CI 1·00–1·12; p = 0·046, n = 13933), with little evidence of heterogeneity (I² 7·1%, p = 0·33). Two studies26,27 contributed about 10% weight to the overall analysis. Exclusion of these had little effect on the overall result. In the 38 chemotherapy trials, median follow-up was 6·7 months (IQR 3·4–15·7) in the erythropoiesis-stimulating agent arm and 8·4 months (3·7–19·1) in the control arm. The combined HR was 1·04 (95% CI 0·97–1·12; p = 0·26, n = 10441), with little evidence of heterogeneity between trials (I² 5·3%, p = 0·38). Two studies28,29 contributed about 10% weight to the overall analysis. Exclusion of any individual study did not greatly change the combined estimate.

Results for mortality during the active study period for all patients with cancer were stratified by study characteristics (figure 4) and patient characteristics explained by the inclusion of trials with 2:1 randomisation and trials including more than one arm of erythropoiesis-stimulating agents. Median age at randomisation was 60·6 years (IQR 51·5–69·2) for patients treated with erythropoiesis-stimulating agents and 59·8 years (50·8–68·1) for those in the control groups. Median haemoglobin concentration at baseline was 106 g/L (96–121) in patients treated with erythropoiesis-stimulating agents and 108 g/L (96–125) in those in the control groups. The most frequent tumours were breast cancer (4302 [31%] of 13933) and lung cancer (3076 [22%]).

In the assessment of mortality during the active study period, median follow-up of all patients assigned to treatment with erythropoiesis-stimulating agents was 3·7 months (IQR 2·8–5·1) and 3·9 months (2·9–5·3) for those in the control groups. The combined HR was 1·17 (95% CI 1·06–1·28; p = 0·003; figure 2). Trial results were homogeneous (I² 9%, p = 0·87) and the results with fixed-effects and random-effects models were identical. Two studies24 contributed more than 10% weight to the overall analysis. Results were robust when we excluded one study at a time. In 38 chemotherapy trials, 5676 patients were randomly assigned to erythropoiesis-stimulating agents and 4765 to control. Median follow-up of patients in chemotherapy trials was 4·1 months (IQR 3·0–5·6) in the erythropoiesis-stimulating agent groups and 4·3 months (3·4–5·7) in the control groups. The combined HR was 1·10 (95% CI 0·98–1·24; p = 0·12; figure 3), with little evidence of heterogeneity between trials (I² 0%, p = 0∙72). One study25 contributed 20% weight to the overall analysis; exclusion of this study reduced the overall HR to 1·03 (0·90–1·18); and exclusion of other studies did not substantially affect the results. Similarly, results changed little when we excluded patients who had not been given chemotherapy in trials classified as chemotherapy trials.

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Results did not change much when we included available used different statistical models or adjusted for baseline were similar (webappendix pp 28–41).

Of note, erythropoiesis-stimulating agents were not admin-
istered exactly according to these indications in any of the trials. Results from stratified analyses for overall survival were given according to Food and Drug Administration licensing indications for November, 2007, and July, 2008 whether or not erythropoiesis-stimulating agents differences were attenuated when we adjusted for other characteristics (planned dose of erythropoiesis-stimulating agent, endpoint of study, calendar year of last patient randomised). There was some evidence to suggest a substantial effect in patients with low baseline haematocrits (figure 5). Conversely, these drugs did not seem to increase mortality in patients with a history of thromboembolic events (figure 5). Effects tended to be pronounced in trials of high quality (ie, placebo-controlled, designed for overall survival, adequate reporting of concealment of allocation) but formal tests of interaction were not significant (p>0·20). There was little evidence for a difference in effects on mortality during the active study period whether or not erythropoiesis-stimulating agents were not signifi cant (p>0·20). There was little evidence for a difference in effects across different patient groups and trials. In particular, although mortality during the active study periods was less markedly increased in patients given chemotherapy than those given other treatments, this difference is compatible with random variation.

Our analysis has several strengths. It was based on individual patient data from 13 933 patients enrolled in randomised trials done by manufacturers and independent investigators. The main analyses were done in duplicate by two independent, experienced groups. Although the studies included clinically diverse populations and different treatment regimens of erythropoiesis-stimulating agents, there was little heterogeneity between results of different trials, and results were robust when subjected to various sensitivity analyses. Few modifiers of the effects of erythropoiesis-stimulating agents on mortality were identifi ed. In view of the large dataset analysed, large differences were unlikely to be missed. However, we acknowledge that small differences cannot be excluded with certainty even in this study. Data were not available for some trials, particularly randomised controlled trials with radiotherapy or radiochemotherapy.90,97 Inclusion of these studies with the published results did not, however, substantially change combined estimates. Only a few trials examined indications for erythropoiesis-stimulating agents that were similar to the approved indications for a survival probability of 70%.

With an underlying survival probability of 95% at 1 year, the NNTH is 34 (19–94), and 24 (14–67) for a survival probability of 80%, the NNTH is 24 (14–67).

Discussion

Erythropoiesis-stimulating agents caused an estimated 17% increase in mortality relative to control during the active study periods in all patients with cancer and a 10% increase in relation to control in those undergoing chemotherapy. There was little evidence for differences in effects across different patient groups and trials. In particular, although mortality during the active study periods was less markedly increased in patients given chemotherapy during the active study periods (HR 1·17, 95% CI 1·06–1·30) to

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Figure 4: Mortality in all patients with cancer during active study periods, stratified by study characteristics

Solid circles represent subgroup hazard ratios (HRs). Horizontal lines indicate 95% CIs. The p value for interaction is based on fixed-effects Cox model stratified by study. ESA=erythropoiesis-stimulating agents. n=number of deaths. N=number of patients.
indications defined by the Food and Drug Administration, and our ability to detect differences between on-label and off-label use was therefore restricted.

By contrast with literature-based meta-analyses, which are restricted to aggregate data at study level, we could consider prognostic factors at the patient level in this meta-analysis of individual patient data. Subgroups of patients with unknown or missing values for a variable are shown but are excluded from the interaction test. ESA=erythropoiesis-stimulating agents. n=number of deaths. N=number of patients.

treatment with erythropoiesis-stimulating agents were more pronounced in analyses restricted to active study periods than the analyses of overall survival, which included additional follow-up. Previous literature-based meta-analyses had to rely on reported results, with absent or inconsistent reporting of survival. Among the reports identified for 51 published studies we analysed, data for survival were not reported in five, data for mortality during the active study period were reported in 19, data for overall survival were reported in 14, and data for both endpoints were reported in 13. Previous meta-analyses combined results for mortality during the active study periods with data for overall survival, which mitigated the noted increase in mortality associated with erythropoiesis-stimulating agents.

Some study authors argued that poor study designs could have introduced bias and, in particular, baseline imbalances favouring controls might at least to some extent explain the increased mortality with erythropoiesis-stimulating agents. In this meta-analysis, effects tended to be increased in studies of good quality, and we found no evidence that baseline imbalances in prognostic factors affected results. High haemoglobin concentrations induced by erythropoiesis-stimulating agents, particularly when greater than 150 g/L, might impair tumour control or increase the risk of fatal thromboembolic and cardiovascular events. Direct comparison of different target haemoglobin concentrations in patients with renal impairment showed increased mortality in patients treated to achieve high haemoglobin concentrations and those treated with high doses of erythropoiesis-stimulating agents.

We noted little evidence for an interaction between treatment with erythropoiesis-stimulating agents, haemoglobin concentration at baseline, target haemoglobin concentrations, planned doses of erythropoiesis-stimulating agents, and mortality. Patients with low haematocrits (<0.235) at baseline and being given erythropoiesis-stimulating agents had an increased risk of death compared with other subgroups: low haematocrits might be a marker for advanced cancer and increased vulnerability to the detrimental effects of erythropoiesis-stimulating drugs. Patients with increased frequency of treatments with erythropoiesis-stimulating agents had a reduced likelihood of death compared with others, yet no clear dose-response association was noted, and the association was confounded by other study characteristics.

Other explanations relate to effects of these drugs on the vascular system and tumour tissue. Increasing evidence suggests that erythropoiesis-stimulating agents might cause thromboembolic and cardiovascular events independently of haemoglobin concentrations. In our analysis, patients with previous thromboembolic events being treated with erythropoiesis-stimulating agents seemed to be protected against an increase in mortality associated with these agents. Prophylactic anticoagulation during cancer treatment in patients with previous
thromboembolic events might have protected them against the thrombogenic effects of erythropoiesis-stimulating agents. A randomised trial in critically ill patients showed that those undergoing treatment with heparin did not have an increased risk of developing thromboembolic complications when treated with erythropoiesis-stimulating agents. Of note, patients with a history of thromboembolic events were equally likely to receive the study drugs and the proportion of those with a history of thromboembolic events was well balanced between study arms. This finding might nevertheless be due to chance. Whether endogenous or exogenous erythropoietins stimulate proliferation of cancer cells expressing erythropoietin receptors is still undergoing debate. However, epoetin-receptor status of tumours was not assessed in the trials included in our meta-analysis.

Whether erythropoiesis-stimulating agents are safer in patients undergoing chemotherapy than in those undergoing radiotherapy, chemotherapy, or no anticancer treatment is a matter of debate. These drugs increased mortality in patients undergoing chemotherapy by 10%. Statistically, the estimated mortality increase in chemotherapy trials is compatible with that in other trials (figure 4). Clinically, patients not given myelosuppressive anticancer treatment are more likely to achieve higher haemoglobin concentrations than those who are not, and might therefore be at increased risk of thromboembolic events and impaired tumour control. The difference between chemotherapy trials and those in patients given other anticancer treatments might thus be real, but have been missed even in this large collaborative study. The increase in mortality associated with erythropoiesis-stimulating agents might be less pronounced or even absent in cancer patients given chemotherapy than in those undergoing other anticancer treatments.

In conclusion, the findings of this individual patient data meta-analysis show that erythropoiesis-stimulating agents increase mortality in all patients with cancer, and a similar increase might exist in patients on chemotherapy. Most randomised trials and previous meta-analyses have shown that erythropoiesis-stimulating agents increase haemoglobin concentrations, reduce the need for transfusions, and reduce fatigue. In clinical practice, the increased risks of death and thromboembolic events should be balanced against the benefits of treatment with erythropoiesis-stimulating agents, taking into account each patient's clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumour progression, and meta-analyses similar to this one will address these questions. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of erythropoiesis-stimulating agents on thrombogenesis and their potential effects on tumour growth.

Contributors
JB, ME, GS, and ST wrote the first draft of the study protocol. JB, CB, MC, BD, ME, MF, AE, MP, DR, MS, GS, JS, DS, ST, OW, and MZ contributed to the final version. JB and OW did literature searches and selected studies. JB and SK extracted additional data. CB, MZ, and JB did the data management, and KS, GS, CB, ST, JB, and MZ did the statistical analyses. IR-C, MM, VM, GT, and MU contributed the data from trials they did. JB, ME, GS, ST, AE, JS, and MF wrote the first draft of the report, and all authors contributed to the final version. ME and AE supervised the study.

Acknowledgments
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