Authors' objectives
To test the hypothesis that albumin administration is not associated with excess mortality.

Searching
Published and unpublished trials were identified by searching MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and the Medical Editors Trial Amnesty. Conference reports, abstracts, compilations of references, and full-text journal articles were also accessed on the Internet using a variety of search engines (AltaVista, Northern Light, HotBot and Excite).

The reviewers manually searched JAMA, the New England Journal of Medicine, Lancet and BMJ from January 1990 to November 2000. Albumin suppliers, and the authors of published randomised trials relating to albumin, were also consulted. Finally, the reference citations in previous meta-analyses, including those in the Cochrane Database of Systematic Reviews (both completed reviews and protocols), review articles, and other reports investigating albumin, were examined. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
The included trials had to compare albumin therapy with either crystalloid therapy, no therapy with exogenous purified albumin, or a lower dose of exogenous purified albumin. Fluid management regimens and concomitant therapies varied widely.

In 7 trials, in addition to the fluid regimen under study, both the albumin and control groups received exogenous purified albumin for the following: intra-operative fluid expansion; post-operative volume expansion; plasma volume replacement on the second postburn day; cardiopulmonary bypass pump priming; volume expansion after treatment failure in high-risk neonates; and adjunctive treatment of patients requiring paracentesis for relief of tense ascites. In 21 included trials, both groups received blood products as concomitant therapy.

Participants included in the review
The authors placed no restrictions on the clinical indication for albumin administration or therapeutic intent, such as volume expansion, correction of hypoalbuminaemia, haemodilution, or maintenance of colloid osmotic pressure.

Fifty-five trials were included: 27 involved surgery or trauma; 4 involved burns; 5 involved hypoalbuminaemia; 6 involved high-risk neonates; 5 involved ascites; and 8 involved other indications. The latter group comprised 2 trials of acute respiratory stress, 2 trials of hyperbilirubinaemia, and one trial each of septic and hypovolemic shock, acute ischaemic stroke, vascular leak syndrome, and ovarian hyperstimulation syndrome.

Outcomes assessed in the review
The primary outcome measure used in the review was mortality.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the trials for inclusion, with differences in interpretation resolved by discussion. The reviewers were not blinded to the authors, institutions, journal, or identity of the treatment groups.
Assessment of study quality
For each paper, the authors determined whether blinding had taken place. The method used to conceal the randomised group allocation was then classified as adequate, inadequate, or unclear using the criteria described by Schulz et al. (see Other Publications of Related Interest no. 1). The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data from the included papers, with differences in interpretation resolved by discussion. Data were extracted on the following: reference details; clinical setting; albumin regimen; study end points; whether there was blinding; classification of allocation concealment; mortality end point, and whether patients crossed over groups.

Methods of synthesis
How were the studies combined?
Where between-trial heterogeneity was found to be non significant, the RRs and 95% confidence intervals (CIs) from the individual trials were pooled using a fixed-effect model.

How were differences between studies investigated?
The between-study heterogeneity was assessed using the method described by DerSimonian and Laird (see Other Publications of Related Interest no.2). Sensitivity analyses were planned and conducted to investigate the effects of the following methodologic quality attributes on outcome: blinding, allocation concealment method, mortality as a study end point, and crossover. Small-trial bias was tested using the technique described by Egger and colleagues (see Other Publications of Related Interest no.3).

Results of the review
Data on mortality were available for 55 trials involving 3,504 randomly-assigned patients. Forty-two of these trials included at least one death, thus allowing the relative risk (RR) to be calculated.

Blinding.
Seven of the 55 (13%) trials included some form of blinding. The study participants who were blinded included the surgeon and anaesthetist; the investigators monitoring the patients; the personnel involved in patient management, except for the perfusionist; caretakers; the treating physicians, study physicians, and study dietitian; all investigators; or the investigators who performed and analysed cerebral blood flow and blood volume measurements.

Allocation concealment.
Of the 55 included trials, the concealment of randomised group allocation was adequate in 21 (38%), inadequate in 4 (7%), and unclear in 30 (55%).

Pooled RR for mortality.
Between-study heterogeneity was not significant for any group. A fixed-effect model was used to pool the RRs.

For all 42 trials reporting at least 1 death, the RR was 1.11 (95% CI: 0.95, 1.28).

For surgery or trauma (20 trials), the RR was 1.12 (95% CI: 0.85, 1.46).

For burns (4 trials), the RR was 1.76 (95% CI: 0.97, 3.17).

For hypoalbuminaemia (4 trials), the RR was 1.59 (95% CI: 0.91, 2.78).

For high-risk neonates (6 trials), the RR was 1.19 (95% CI: 0.78, 1.81).
For ascites (4 trials), the RR was 0.93 (95% CI: 0.67, 1.28).

For other indications (4 trials), the RR was 0.91 (95% CI: 0.67, 1.22).

Small-trial bias.

Significant small-trial bias favouring the control group was detected (P=0.03). To evaluate the magnitude of the small-trial bias effect, the trials were stratified according to whether the total number of randomised patients was less than 100, or at least 100. The pooled RR for the trials with at least 100 patients was lower than that for trials with less than 100 patients; this was found both among all trials and across all strata of methodologic quality.

Authors' conclusions
Overall, albumin was not found to have an effect on mortality; any such effect may, therefore, be small. This finding supported the safety of albumin. The influence of methodologic quality on the RR for death suggested the need for further well-designed clinical trials.

CRD commentary
This was a fairly well-conducted systematic review with well-defined inclusion and exclusion criteria. A comprehensive search of the literature was undertaken, which involved searches of several databases and the Internet, handsearches of relevant journals, examination of reference lists, plus contact with the manufacturers. Though the inclusion criteria were rather broad, they were independently applied by two reviewers. Not all aspects of validity were assessed, the effects of concealment of treatment allocation and blinding were determined by sensitivity analysis. Appropriate details of the individual included studies were presented in the text and in tabular format.

The calculation of the RRs and 95% CIs when heterogeneity was proven to be statistically non significant was appropriate. Issues of publication bias were also addressed. The conclusions were supported by the data presented in the review.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that 'further well-designed, adequately powered, blinded, randomised trials are warranted to resolve the continued uncertainty about the efficacy of albumin in certain clinical situations and patient populations'.

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