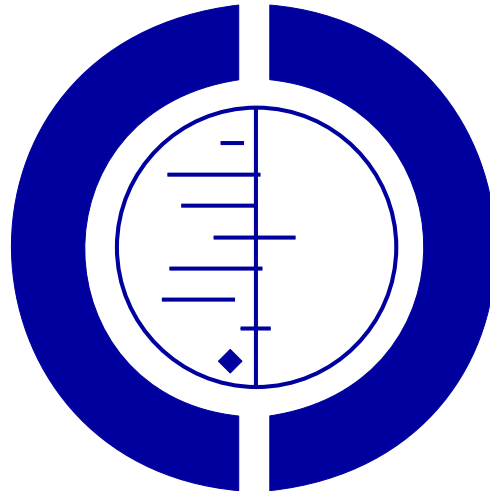


# Human albumin solution for resuscitation and volume expansion in critically ill patients (Review)

The Albumin Reviewers (Alderson P, Bunn F, Li Wan Po A, Li L, Roberts I, Schierhout G)



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## ABSTRACT

### Background

Human albumin solutions are used in a range of medical and surgical problems. Licensed indications are the emergency treatment of shock and other conditions where restoration of blood volume is urgent, burns, and hypoproteinaemia. Human albumin solutions are more expensive than other colloids and crystalloids.

### Objectives

To quantify the effect on mortality of human albumin and plasma protein fraction (PPF) administration in the management of critically ill patients.

### Search strategy

We searched the Cochrane Injuries Group trials register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and BIDS Index to Scientific and Technical Proceedings. Reference lists of trials and review articles were checked, and authors of identified trials were contacted. The search was last updated in August 2004.

### Selection criteria

Randomised controlled trials comparing albumin/PPF with no albumin/PPF, or with a crystalloid solution, in critically ill patients with hypovolaemia, burns or hypoalbuminaemia.

### Data collection and analysis

We collected data on the participants, albumin solution used, mortality at the end of follow up, and quality of allocation concealment. Analysis was stratified according to patient type.

### Main results

We found 32 trials meeting the inclusion criteria and reporting death as an outcome. There were 1632 deaths among 8452 trial participants.

For hypovolaemia, the relative risk of death following albumin administration was 1.01 (95% confidence interval 0.92, 1.10). This estimate was heavily influenced by the results of the SAFE trial which contributed 91% of the information (based on the weights in the meta-analysis). For burns, the relative risk was 2.40 (1.11, 5.19) and for hypoalbuminaemia the relative risk was 1.38 (0.94, 2.03). There was no substantial heterogeneity between the trials in the various categories (chi-square = 21.86, df = 25, p = 0.64). The pooled relative risk of death with albumin administration was 1.04 (0.95, 1.13).

### Authors' conclusions

For patients with hypovolaemia there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline. There is no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminaemia. The possibility

that there may be highly selected populations of critically ill patients in which albumin may be indicated remains open to question. However, in view of the absence of evidence of a mortality benefit from albumin and the increased cost of albumin compared to alternatives such as saline, it would seem reasonable that albumin should only be used within the context of well concealed and adequately powered randomised controlled trial.

## PLAIN LANGUAGE SUMMARY

There is no evidence that giving human albumin to replace lost blood in critically ill or injured people improves survival when compared to giving saline.

Trauma, burns or surgery can cause people to lose large amounts of blood. Fluid replacement, giving fluids intravenously (into a vein), is used to help restore blood volume and hopefully reduce the risk of dying. Blood products (including human albumin), non-blood products or combinations can be used. The review of trials found no evidence that albumin reduces the risk of dying. Albumin is very expensive in which case it may be better to use cheaper alternatives such as saline for fluid resuscitation.

## BACKGROUND

In patients with acute and chronic illness, serum albumin concentration is inversely related to mortality risk. A systematic review of cohort studies meeting specified criteria estimated that, for each 2.5 g/L decrement in serum albumin concentration, the risk of death increases by between 24% and 56% (Goldwasser 1997). The association persists after adjusting for other known risk factors and pre-existing illness, suggesting a direct protective effect of the albumin molecule (Goldwasser 1997). Largely as a result of these observations, human albumin solutions are now used in the management of a diverse range of medical and surgical problems. Published indications for human albumin solution include the emergency treatment of shock and other conditions where restoration of blood volume is urgent, the acute management of burns, and clinical situations associated with hypoproteinaemia (ABPI 1998).

In comparison with other colloidal solutions and with crystalloid solutions, human albumin solutions are expensive (McClelland 1990). Volume for volume human albumin solution is twice as expensive as hydroxyethyl starch, and over thirty times more expensive than crystalloid solutions such as sodium chloride or Ringer's lactate. Because of the high cost and limited availability of human albumin, it is particularly important that its use should be restricted to the indications for which it has shown to be effective. To assess the effectiveness and safety of human albumin solutions in the management of critically ill patients, particularly those with hypovolaemia from injury or surgery, burns and hypoproteinaemia, a systematic review of randomised controlled trials was conducted.

## OBJECTIVES

To quantify the effect on mortality of human albumin administration in the management of critically ill patients.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

We sought to identify all randomised controlled trials of human albumin or plasma protein fraction (PPF) administration (albumin/PPF versus no albumin/PPF, or a crystalloid solution).

### Types of participants

Critically ill patients with hypovolaemia, burns or hypoproteinaemia. Trials involving patients receiving pre-operative volume loading or haemodilution, and trials of albumin administration during paracentesis, were excluded.

### Types of intervention

Human albumin solution or plasma protein fraction (PPF).

### Types of outcome measures

The principal outcome measure was mortality from all causes assessed at the end of the follow up period scheduled for each trial.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Injuries Group methods used in reviews.

Trials were identified by computerised searches of CENTRAL, the Cochrane Controlled Trials Register, and MEDLINE using the following search terms: Exploded MeSH terms ALBUMINS,

PLASMA SUBSTITUTES, AND PLASMA and the free text terms: volume next replacement, human next albumin, frozen next plasma, fresh next plasma, plasma next protein, low next albumin, and hypoalbumin\*. EMBASE was searched using a search strategy developed by Carol Lefebvre, information scientist at the UK Cochrane Centre, and a copy of this can be obtained from the Review Group Co-ordinator.

Trials were also identified using BIDS Index to Scientific and Technical Proceedings and by hand searching 29 international journals and the proceedings of several international meetings on fluid resuscitation; by checking the reference lists of all trials and review articles; and by contacting the authors of all identified trials asking them about any other published or unpublished trials that may have been conducted. There were no language restrictions. To identify unpublished trials we searched the register of the Medical Editors' Trial Amnesty, and contacted the Medical Directors of Bio Products Laboratory (Zenab), Centeon Limited (Albuminar), and Alpha Therapeutic UK Limited (Albutein).

An updated search was carried out using the following electronic databases and search strategies in September 2002. Searches of web-based trials databases and the internet in general were also carried out.

Cochrane Injuries Group Trials Register 09/2002

#1 (albumin\* or colloid\* or ppf or dextran\* or gelatin\* or gentran\* or haemaccel\* or hemacell\* or hetastarch\* or pentastarch\* or pentaspan)  
#2 (volume or fluid\*) and (resuscitat\* or restor\* or replac\*)  
#3 #1 and #2

Cochrane Central Register of Controlled Trials 2002 issue 3 (CD)

Pubmed to 2002/09 (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>)

National Research Register 2002 issue 3

#1 explode "Fluid Therapy" / all SUBHEADINGS  
#2 explode "Albumins" / all SUBHEADINGS  
#3 explode "Plasma Substitutes" / all SUBHEADINGS  
#4 explode "Saline Solution Isotonic" / all SUBHEADINGS  
#5 explode "Isotonic Solutions" / all SUBHEADINGS  
#6 explode "Colloids" / all SUBHEADINGS  
#7 colloid\* or albumin\* or dextran\* or gelatin\* or gentran\* or h?emaccel\* or pentastarch\* or pentaspan\* or hetastarch\*  
#8 crystalloid\* or ringer\* or hartman\* or sodium\* or potassium\* or salin\*  
#9 ppf or (plasma next protein\*)  
#10 (fluid near therap\*) or (fluid near restor\*) or (fluid near substitut\*) or (fluid near resuscitat\*) or (fluid near replac\*)  
#11 (volume near therap\*) or (volume near restor\*) or (volume near substitut\*) or (volume near resuscitat\*) or (volume near replac\*)

#12 (#7 in ti) or (#7 in ab) or (#8 in ti) or (#8 in ab) or (#9 in ti) or (#9 in ab) or (#10 in ti) or (#10 in ab) or (#11 in ti) or (#11 in ab)

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 RCT filter (Clarke 2001)

#15 #13 and #14

EMBASE to 2002 September week 1 (OVID)

#1 exp Fluid Therapy/

#2 exp Albumin/

#3 exp Plasma Substitute/

#4 exp Colloid/

#5 exp Isotonic Solution/

#6 (colloid\$ or albumin\$ or dextran\$ or gelatin\$ or gentran\$ or haemaccel\$ or hemacell\$ or pentastarch\$ or pentaspan\$ or hetastarch\$).ti,ab.

#7 (crystalloid\$ or ringer\$ or hartman\$ or salin\$).ti,ab.

#8 (ppf or plasma next protein\$).ti,ab.

#9 ((fluid adj5 therap\$) or (fluid adj5 restor\$) or (fluid adj5 substitut\$) or (fluid adj5 resuscitat\$) or (fluid adj5 replac\$)).ti,ab.

#10 ((volume adj5 therap\$) or (volume adj5 restor\$) or (volume adj5 substitut\$) or (volume adj5 resuscitat\$) or (volume adj5 replac\$)).ti,ab.

#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

#12 exp Randomized Controlled Trial/

#13 randomi\$ or (single adj blind\$) or (double adj blind\$) or (controlled adj trial\$)

#14 #12 or #13

#15 #14 and #11

Science Citation Index to September 2002 (Web of Science)

(colloid OR colloids OR albumin OR albumins OR plasma substitut\* OR plasma protein\* OR ppf OR dextran OR gelatin\* OR gentran\* OR hemacell\* OR haemaccel\* OR pentastarch\* OR pentaspan\* OR hetastarch\*) AND (fluid\* OR volume\*) AND trial\*

## METHODS OF THE REVIEW

One reviewer (a different person for different databases) scanned the titles and abstracts of reports identified by electronic searching to produce a list of possibly relevant reports. Two reviewers (PA and IR) then checked this list to determine which articles to retrieve in full. Disagreements were resolved by discussion.

The same two reviewers then applied the selection criteria, again resolving disagreements by discussion. They then both extracted data on study design, allocation concealment, participants, interventions and mortality. One reviewer (IR) put the data into Review Manager while the other (PA) checked it against his data extraction.

Where clarification on any aspect of the study was needed one reviewer sought to contact the author of the trial.

Relative risks and 95% confidence intervals for mortality were calculated for each trial on an intention to treat basis. Heterogeneity between trials was tested using a Chi-squared test, where  $p$  less than or equal to 0.05 was taken to indicate significant heterogeneity. As long as statistical heterogeneity did not exist, for dichotomous data, summary relative risks and 95% confidence intervals were calculated using a fixed effects model. In the event of statistical heterogeneity, if the source of heterogeneity could obviously be related to patient type, or allocation concealment, we stratified the analyses on that dimension.

## DESCRIPTION OF STUDIES

A total of 37 randomised controlled trials were identified that met the study inclusion criteria. Mortality data were available either from the published report or on contact with the authors of 32 of these trials. The five trials for which mortality data could not be obtained (McNulty 1993; Skillman 1975; Ernest 1999; Ernest 2001; Oca 1999) included a total of 124 randomised patients, comprising 8% of the total number of randomised patients in all trials meeting the study inclusion criteria. One of the trials was an unpublished trial registered in the Medical Editors' Trial Amnesty. Further details about this trial, including data on mortality, were obtained directly from the trialist. In six trials there were no deaths in either the intervention or comparison groups. The trial by Lucas et al was reported in five publications. An early report gave the mortality data for 52 randomised patients, 27 allocated to receive albumin, 25 allocated to receive no albumin (Lucas 1978). Subsequent publications indicated that recruitment to the trial continued until 94 patients were randomised. Mortality data for all the 94 patients were not published, nor were they available on contact with the author. Consequently the outcome data for the 52 patients are presented. For the 25 included trials in which there were one or more deaths in either the intervention or control groups, allocation concealment involved a method that would be expected to reduce the risk of foreknowledge of treatment allocation (pharmacy controlled randomisation or serially numbered sealed opaque envelopes) in 13 trials, was unclear in eight trials, and inadequate in four trials.

## METHODOLOGICAL QUALITY

**Bland 1973**  
Randomised control trial. Therapy cards were randomised in pairs matched for weight. Method of allocation concealment was not described.

**Bland 1976**

This study is reported as randomised but the method of allocating random numbers and method of allocation concealment are unknown.

**Boldt 1993**  
Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

**Boutros 1979**  
The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

**Brown 1988**  
The random sequence was generated using random number tables. No allocation concealment.

**Ernest 1999**  
Randomisation was done by the hospital chart number (odd/even).

**Ernest 2001**  
Randomisation was done by the hospital record number (odd/even).

**Foley 1990**  
Patients were randomly assigned to either a treatment or non treatment group by medical record number.

**Gallagher 1985**  
Randomisation and allocation concealment were by computerised system.

**Golub 1994**  
Random sequence was computer generated. Allocation concealment was by the use of sealed opaque envelopes.

**Goodwin 1983**  
Randomisation was according to random number tables. The methods of allocation concealment were unknown.

**Greenhalgh 1995**  
Randomisation scheme controlled by the pharmacy

**Greenough 1993**  
Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

**Grundmann 1982**  
The study is reported as prospectively randomised, but the methods of randomisation and allocation concealment are unknown.

**Jelenko 1978**  
The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

**Kanarek 1992**  
Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

**Lowe 1977**

The method of allocating random numbers is unknown. Sealed envelopes were used to ensure allocation concealment.

Lucas 1978

Allocation was based on the last digit of each patient's case number. Ninety four patients were randomised in total but the number of deaths was not reported in the final report. However, in a preliminary report, based on 52 of the randomised patients, deaths were reported.

McNulty 1993

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

Nielsen 1985

This study is reported as randomised but the method of allocation concealment is not described.

Nilsson 1980

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

Oca 1999

Randomisation was done by sequentially numbered, sealed, opaque envelopes.

Pockaj 1994

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

Prien 1990

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

Rackow 1983

Randomisation was according to a pre-determined randomisation schedule, but the methods and the allocation concealment are unknown.

Rubin 1997

Allocation concealment was by a sealed opaque envelope system in the hospital pharmacy.

SAFE 2004

Central randomisation accessed on the internet through a secure website with use of a minimisation algorithm. Blinding was assured through the use of specially designed masking cartons and specially designed and manufactured administration sets. The authors report that the effectiveness of the blinding was confirmed in a formal study before the trial was initiated.

Shah 1977

Randomised controlled trial. Allocation by sealed envelope.

Skillman 1975

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

So 1997

Randomised controlled trial. Allocation concealment was by computerised system.

Tollofsrud 1995

The method of generating random numbers is unknown. Allocation concealment was by sealed opaque envelopes.

Virgilio 1979

Randomisation was determined using random number tables. Methods of allocation concealment are unknown.

Woittiez 1998

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

Wojtysiak 1992

Randomisation was determined using random number tables. Allocation concealment was inadequate.

Woods 1993

Patients with even hospital numbers were allocated to the group receiving albumin, while those with odd hospital numbers were allocated to the group not receiving supplemental albumin.

Zetterstrom 1981a

Patients were randomly divided into two groups. Allocation concealment was by the use of sealed opaque envelopes.

Zetterstrom 1981b

Patients were randomly divided into two groups. Allocation concealment was by the use of sealed opaque envelopes.

## RESULTS

For hypovolaemia the pooled relative risk of death following albumin administration was 1.01 (95% confidence interval 0.92, 1.10). This estimate was heavily influenced by the results of the SAFE trial which received 91% of the weight. For burns the relative risk was 2.40 (1.11, 5.19), and for hypoalbuminaemia the relative risk was 1.38 (0.94, 2.03). There was no substantial heterogeneity between the trials in the various categories (chi-square = 21.86, df = 25, p = 0.64). The pooled relative risk of death with albumin administration was 1.04 (0.95, 1.13).

## DISCUSSION

There is no evidence that albumin reduces mortality in patients with hypovolaemia, burns and hypoproteinaemia. For patients with burns and hypoproteinaemia, there is a suggestion that albumin administration may increase mortality.

Mortality was selected as the outcome measure in this systematic review for several reasons. In the context of critical illness, death or survival is a clinically relevant outcome that is of immediate importance to patients, and data on death are reported in nearly all

studies. Furthermore, one might expect that mortality data would be less prone to measurement error or biased reporting than would data on pathophysiological outcomes. The use of a pathophysiological end-point as a surrogate for an adverse outcome assumes a direct relationship between the two, an assumption that may sometimes be inappropriate. Finally, when trials collect data on a number of physiological end points, there is the potential for bias due to the selective publication of end points showing striking treatment effects. Because we obtained mortality data for all but four of the included trials, the likelihood of bias due to selective publication of trial outcomes is minimal.

Although publication bias is a potent threat to the validity of systematic reviews, it is unlikely to have had an important impact in this study. There was no evidence of funnel plot asymmetry on visual inspection. In some of the trials included in this review, allocation concealment was inadequate or was unclear. As a result, it is possible that more severely ill patients were preferentially allocated to the albumin treated group which may account for the increased mortality risk in this group. Nevertheless, when the analyses were repeated, including only those trials in which allocation concealment involved a method that would be expected to reduce the risk of foreknowledge of treatment allocation, the point estimates were little different.

Because many of the trials included in this meta-analysis are small and many are poorly concealed, the results must be interpreted with caution. The SAFE trial, however, is a notable exception. The SAFE trial included a total of 6997 randomised participants, allocation was well concealed, the use of a minimisation algorithm helped to ensure that baseline characteristics were well balanced, vigorous attempts were made to ensure that the participating clinicians were blind to the type of fluid that was administered, and an intention-to-treat analysis was undertaken. The SAFE trial provided no evidence that albumin reduced mortality in patients with hypovolaemia, although the possibility of a modest benefit or harm could not be excluded.

This systematic review was first updated in November 2001. One additional trial was identified and included (Bland 1973). This trial compared albumin and dextrose infusions in new-born infants with low cord serum protein levels who were considered to be at risk of respiratory distress. This trial meets the eligibility criteria for the review (hypo-proteinaemia) but had been overlooked in the original search. However, the inclusion of this trial does not change the conclusions of the review. The review was most recently updated in August 2004, following the publication of the SAFE trial.

## **AUTHORS' CONCLUSIONS**

### **Implications for practice**

For patients with hypovolaemia there is no evidence that albumin

reduces mortality when compared with cheaper alternatives such as saline. There is no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminaemia and a suggestion that albumin may increase the risk of death.

### **Implications for research**

The possibility that there may be highly selected populations of critically ill patients in which albumin may be indicated remains open to question. However, in view of the absence of evidence of a mortality benefit from albumin and the increased cost of albumin compared to alternatives such as saline, it would seem reasonable that albumin should only be used within the context of well concealed and adequately powered randomised controlled trial.

## **NOTES**

Please note that this review was also published in the BMJ 1998;317:235-240.

## **FEEDBACK**

### **Human albumin solution**

#### **Summary**

1. It would be helpful to state that this review was published in the BMJ in 1998, to summarise the subsequent correspondence in print and on the BMJ website, and to note the respects (if any) in which this Cochrane review differs from the BMJ publication.
2. It would be valuable to summarise the report of the Committee for Safety of Medicines (CSM) on this review in the Comments and Criticisms section, with a rejoinder by the authors.
3. Because mortality was not the primary endpoint in any of the trials reviewed, it would be useful to note the primary outcomes of each trial, under 'characteristics of included trials'.
4. It would be helpful if the number of participants in each arm of each reviewed trial appeared under 'characteristics of included trials.'

#### **Author's reply**

1. We agree that it is important to direct the reader to other published versions of the review and will ensure that readers are alerted to the BMJ publication. We do not think it is appropriate to summarise the correspondence in response to this review, as to do so would run the risk of misrepresenting the views of the correspondents. At the time of first publication the Cochrane review was identical to the review published in the BMJ. However, the Cochrane review will be regularly updated to take account of new information from randomised controlled trials.
2. The Cochrane Database of Systematic Reviews is an international database and for this reason we believe that it would be

inappropriate to give undue emphasis to the deliberations of the British Committee on Safety of Medicines (CSM).

3. Mortality was recorded in all but two of the trials included in our systematic review. However, we have no information on whether this was considered by the trialist to be the primary endpoint and would be interested to hear where the author of the comment found this information. How does the author of the comment define a primary endpoint? The concept of a primary endpoint implies a selection within the mind of the trialist of the most important endpoint. We would also ask whether it is appropriate that a process within the mind of a trialist should impact importantly on the estimation of the effect of albumin on mortality, and if so, what is the scientific basis for this.

4. We have included the number of participants in each arm of each reviewed trial in the section 'characteristics of included trials' as suggested.

Contributors

Author of comments: Dr Andrew Herxheimer

Author of Responses: Ian Roberts

### Human albumin solution

Summary

I gather that a further trial - prompted by the review - is now planned and possibly underway in Australasia. If so, I think this should be mentioned, preferably with a link to a record for the trial on the meta-Register of Controlled Trials

Author's reply

Details of this ongoing trial are now in the on-going studies section.

Contributors

Author of comments: Iain Chalmers, UK

Author of response: Ian Roberts, UK

### Human albumin solution

Summary

Human albumin solution for resuscitation and volume expansion in critically ill patients

Summary of comment

1. In the hypovolaemia group, five randomised controlled trials were incorrectly included and should be deleted(1).

2. The Cochrane Albumin Review excluded or omitted extensive randomised controlled trials' evidence in the three categories of indications, namely, hypovolaemia, burns and hypoalbuminaemia(2) and this excluded and omitted evidence indicated that albumin may reduce rather than increase mortality.

(1) Horsey P Albumin and hypovolaemia - is the Cochrane evidence to be trusted? Lancet 2002 359 70-72

(2) Willkes MM and Navickis RJ Patient survival after human albumin administration: a meta-analysis of randomised controlled trials.

Annals of Internal Medicine 2001 135 149-164

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Author's reply

We are grateful to Dr Horsey for his thoughtful comments on our systematic review of albumin administration in critically ill patients. The comments were first made as a commentary in *The Lancet* (2002;359:70-72). Our response to these comments was published in the same issue (*Lancet* 2002;359:72-3). We are pleased that this discussion will now be available to readers of the Cochrane Library.

Dr Horsey feels that some of the trials included under the category 'hypovolaemia' would be more appropriate in a different category. We accept that in some clinical situations hypovolaemia and hypoalbuminaemia co-exist so that deciding which category would be most appropriate is a matter for judgement. Also, as Dr Horesy points out, the relationship between hypovolaemia and low blood pressure can be complicated, and the presence of the latter might not always signify the former. Nevertheless, our judgements about the categories were made without knowledge of the results of the trials and we are reluctant to change these post-hoc.

We are grateful to Dr Horsey for drawing our attention to the meta-analysis by Wilkes et al that was funded by the Plasma Protein Therapeutics Association. Because the inclusion criteria for the Cochrane Injuries Group Albumin Reviewer and the Wilkes reviews are different it does not follow that the two reviews should include the same trials.

We are pleased that our systematic review has stimulated so much interest from the intensive care community. However, it is a cause for concern that four years following the publication of our review, in which we concluded that there is no evidence that albumin administration reduced mortality in critically ill patients and a suggestion that it may increase mortality, that albumin continues to be used and promoted. Hopefully, the SAFE trial ([www.safestudy.net](http://www.safestudy.net)) will provide the evidence needed to resolve this issue

Contributors

Comment: Dr PJ Horsey

Reply: Professor Ian Roberts

### POTENTIAL CONFLICT OF INTEREST

None known.

## ACKNOWLEDGEMENTS

We thank the Intensive Care National Audit & Research Centre in London for help with identifying trials for this review and for their extensive hand searching activities. We are grateful to AJ Woitiez for providing unpublished trial data from the trial that was registered in the Medical Editors' Trial Amnesty. We thank Elizabeth Bryant, Information Officer at Centeon Limited, and Martin O'Fobve at Bio Products Limited, for searching their databases for albumin trials. We thank Anne Greenough for re-examining individual patient records in order to provide data on mortality. We are also grateful to Peter Sandercock for his assistance in the editorial process.

Thanks also to Carol Lefebvre of the UK Cochrane Centre, for help in designing the search strategy and conducting database searches.

## SOURCES OF SUPPORT

### External sources of support

- NHS Research and Development UK

### Internal sources of support

- Institute of Child Health, University College London UK

## REFERENCES

### References to studies included in this review

#### Bland 1973 *{published data only}*

Bland RD, Clarke TL, Harden LB, Meyer JL, Ries JP, Madden WA, Crast FW, Coyer WF, Bass JW. Early albumin infusion to infants at risk for respiratory distress. *Archives of Disease in Childhood* 1973;**48**: 800–805.

#### Bland 1976 *{published data only}*

Bland RD, Clarke TL, Harden LB. Rapid infusion of sodium bicarbonate and albumin into high-risk premature infants soon after birth: A controlled, prospective trial. *American Journal of Obstetrics and Gynecology* 1976;**124**:263–7. 1976109310.

#### Boldt 1993 *{published data only}*

Boldt J, Knothe C, Zickmann B, Andres P, Dapper F, Hempelmann G. Influence of different intravascular volume therapies on platelet function in patients undergoing cardiopulmonary bypass. *Anesthesia and Analgesia* 1993;**76**:1185–90. 1993270221.

#### Boutros 1979 *{published data only}*

Boutros AR, Ruess R, Olson L, Hoyt JL, Baker WH. Comparison of hemodynamic, pulmonary, and renal effects of use of three types of fluids after major surgical procedures on the abdominal aorta. *Critical Care Medicine* 1979;**7**(1):9–13. 1979106434.

#### Brown 1988 *{published data only}*

Brown RO, Bradley JE, Bekemeyer WB, Luther RW. Effect of albumin supplementation during parenteral nutrition on hospital morbidity. *Critical Care Medicine* 1988;**16**:1177–82. 1989052295.

#### Ernest 1999 *{published data only}*

Ernest D, Belzberg AS, Dodek PM. Distribution of normal saline and 5% albumin infusions in septic patients. *Critical Care Medicine* 1999;**27**(1):46–50.

#### Ernest 2001 *{published data only}*

Ernest D, Belzberg AS, Dodek PM. Distribution of normal saline and 5% albumin infusions in cardiac surgical patients. *Critical Care Medicine* 2001;**29**(19):2299–2302.

#### Foley 1990 *{published data only}*

Foley EF, Borlase BC, Dzik WH, Bistran BR, Benotti PN. Albumin supplementation in the critically ill: a prospective randomised trial. *Archives of Surgery* 1990;**125**:739–42. 1990267215.

#### Gallagher 1985 *{published data only}*

Gallagher JD, Moore RA, Kerns D, Jose AB, Botros SB, Flicker S, Naidech H, Clark DL. Effects of colloid or crystalloid administration on pulmonary extravascular water in the postoperative period after coronary artery bypass grafting. *Anesthesia and Analgesia* 1985;**64**: 753–8. 1985249399.

#### Golub 1994 *{published data only}*

Golub R, Sorrento JJ Jr, Cantu R Jr, Nierman DM, Moideen A, Stein HD. Efficacy of albumin supplementation in the surgical intensive care unit: a prospective, randomized study. *Critical Care Medicine* 1994;**22**(4):613–9. 1994192358.

- Goodwin 1983** {published data only}  
Goodwin CW, Dorethy J, Lam V, Pruitt BA Jr. Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury. *Annals of Surgery* 1983;**197**(5):520–31. 1983203066.
- Greenhalgh 1995** {published data only}  
Greenhalgh DG, Housinger TA, Kagan RJ, et al. Maintenance of serum albumin levels in pediatric burn patients: a prospective, randomized trial. *Journal of Trauma* 1995;**39**(1):67-73; discussion 73-4. 1995363875.
- Greenough 1993** {published and unpublished data}  
Greenough A, Emery E, Hird MF, Gamsu HR. Randomised controlled trial of albumin infusion in ill preterm infants. *European Journal of Pediatrics* 1993;**152**:157–9. 1993185716.
- Grundmann 1982** {published data only}  
Grundmann R, Meyer H. The significance of colloid osmotic pressure measurement after crystalloid and colloid infusions. *Intensive Care Medicine* 1982;**8**:179–86. 1983008021.
- Jelenko 1978** {published data only}  
Jelenko C 3rd. Fluid therapy and the HALFD method. *Journal of Trauma* 1979;**19**(11 Suppl):866–7. 1980029813.
- Jelenko C 3rd, Solenberger RI, Wheeler ML, Callaway BD. Shock and resuscitation. III. Accurate refractometric COP determinations in hypovolemia treated with HALFD. *Journal of the American College of Emergency Physicians* 1979;**8**(7):253–6. 1979197471.
- Jelenko C 3rd, Wheeler ML, Callaway BD, Divilio LT, Bucklen KR, Holdredge TD. Shock and resuscitation. II: volume repletion with minimal edema using the “HALFD” (Hypertonic Albuminated Fluid Demand) regimen. *Journal of the American College of Emergency Physicians* 1978;**7**(9):326–33. 1994194739.
- Jelenko C 3rd, Williams JB, Wheeler ML, et al. Studies in shock and resuscitation, I: use of a hypertonic, albumin-containing, fluid demand regimen (HALFD) in resuscitation. *Critical Care Medicine* 1979;**7**(4):157–67. 1979190564.
- Kanarek 1992** {published data only}  
Kanarek KS, Williams PR, Blair C. Concurrent administration of albumin with total parenteral nutrition in sick newborn infants. *Journal of Parenteral and Enteral Nutrition* 1992;**16**:49–53. 1992148989.
- Lowe 1977** {published data only}  
Lowe RJ, Moss GS, Jilek J, Levine HD. Crystalloid versus colloid in the etiology of pulmonary failure after trauma - a randomized trial in man. *Critical Care Medicine* 1979;**7**(3):107–12. 1979168390.
- Lowe RJ, Moss GS, Jilek J, Levine HD. Crystalloid vs colloid in the etiology of pulmonary failure after trauma: a randomized trial in man. *Surgery* 1977;**1**(6):676–83. 1977175168.
- Moss GS, Lowe RJ, Jilek J, Levine HD. Colloid or crystalloid in the resuscitation of hemorrhagic shock: a controlled clinical trial. *Surgery* 1981;**89**(4):434–8. 1981153604.
- Lucas 1978** {published data only}  
Clift DR, Lucas CE, Ledgerwood AM, Sardesai V, Kithier K, Grabow D. The effect of albumin resuscitation for shock on the immune response to tetanus toxoid. *Journal of Surgical Research* 1982;**32**:449–52. 1982218154.
- Johnson SD, Lucas CE, Gerrick SJ, Ledgerwood AM, Higgins. Altered coagulation after albumin supplements for treatment of oligoemic shock. *Archives of Surgery* 1979;**114**:379–83. 1979165094.
- Lucas CE, Bouwman DL, Ledgerwood AM, Higgins R. Differential serum protein changes following supplemental albumin resuscitation for hypovolaemic shock. *Journal of Trauma* 1980;**20**(1):47–51. 1980097223.
- Lucas CE, Weaver D, Higgins RF, Ledgerwood AM, Johnson SD, Bouwman DL. Effects of albumin versus non-albumin resuscitation on plasma volume and renal excretory function. *Journal of Trauma* 1978;**18**:565–70. 1978244737.
- Weaver DW, Ledgerwood AM, Lucas CE, Higgins R, Bouwman DL, Johnson SD. Pulmonary effects of albumin resuscitation for severe hypovolaemic shock. *Archives of Surgery* 1978;**113**:387–92. 1978143847.
- McNulty 1993** {published data only}  
McNulty SE, Sharkey SJ, Asam B, Lee JH. Evaluation of STAT-CRIT Hematocrit Determination in comparison to Coulter and Centrifuge: the effects of isotonic hemodilution and albumin administration. *Anesthesia and Analgesia* 1993;**76**:830–4. 1993220903.
- Nielsen 1985** {published data only}  
Nielsen OM, Engell HC. Effects of maintaining normal plasma colloid osmotic pressure on renal function and excretion of sodium and water after major surgery: a randomised study. *Danish Medical Bulletin* 1985;**32**:182–5. 1985256448.
- Nielsen OM, Engell HC. Extracellular fluid volume and distribution in relation to changes in plasma colloid osmotic pressure after major surgery. A randomised study. *Acta Chirurgica Scandinavica* 1985;**151**:221–5. 1985247186.
- Nielsen OM, Thunedborg P, Jorgensen K. Albumin administration and acute phase proteins in abdominal vascular surgery: a randomised study. *Danish Medical Bulletin* 1989;**36**:496–9. 1990031802.
- Nilsson 1980** {published data only}  
Nilson E, Lamke O, Liljedahl SO, Elfstrom K. Is albumin therapy worthwhile in surgery for colorectal cancer?. *Acta Chirurgica Scandinavica* 1980;**146**:619–22. 1981180051.
- Oca 1999** {published data only}  
\* Oca MJ, Nelson M, Donn SM. Randomized trial of normal saline (NS) versus 5% albumin (ALB) for the treatment of neonatal hypotension. *Pediatric Research*. 1999; Vol. 45:#1265.
- Pockaj 1994** {published data only}  
Pockaj BA, Yang JC, Lotze MT, et al. A prospective randomized trial evaluating colloid versus crystalloid resuscitation in the treatment of the vascular leak syndrome associated with interleukin-2 therapy. *Journal of Immunotherapy* 1994;**15**(1):22–8. 1994153877.
- Prien 1990** {published data only}  
Prien T, Backhaus N, Pelster F, Pircher W, Bunte H, Lawin P. Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. *Journal Clinical Anesthesia* 1990;**2**:317–23. 1991104037.
- Rackow 1983** {published data only}  
Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, het-

- astarch, and saline solutions in patients with hypovolemic and septic shock. *Critical Care Medicine* 1983;**11**(11):839–50. 1984027713.
- Rubin 1997** *{published data only}*  
Rubin H, Carlson S, DeMeo M, Ganger D, Craig R. Randomized, double-blind study of intravenous human albumin in hypoalbuminemic patients receiving total parenteral nutrition. *Critical Care Medicine* 1997;**25**:249–52. 1997186643.
- SAFE 2004** *{published data only}*  
The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine* 2004;**350**:2247–56.
- Shah 1977** *{published data only}*  
Shah DM, Broner BD, Dutton RE, Newell JC, Powers SR. Cardiac output and pulmonary wedge pressure. Use for evaluation of fluid replacement in trauma patients. *Archives of Surgery* 1977;**112**:1161–4. 1978019134.
- Skillman 1975** *{published data only}*  
Skillman JJ, Restall DS, Salzman EW. Randomized trial of albumin vs. electrolyte solutions during abdominal aortic operations. *Surgery* 1975;**78**(3):291–303. 1975219514.
- So 1997** *{published data only}*  
So KW, Fok TF, Ng PC, Wong WW, Cheung KL. Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. *Archives of Diseases of Childhood* 1997;**76**:F43–F46. 1997212330.
- Tollofsrud 1995** *{published data only}*  
Svennevig JL, Tollofsrud S, Kongsgaard U, Noddeland H, Mohr B, Ozer M, Mollnes TE. Complement activation during and after open-heart surgery is only marginally affected by the choice of fluid for volume replacement. *Perfusion* 1996;**11**:326–32.  
  
Tollofsrud S, Svennevig JL, Breivik H, et al. Fluid balance and pulmonary functions during and after coronary artery bypass surgery: Ringer's acetate compared with dextran, polygeline, or albumin. *Acta Anaesthesiologica Scandinavica* 1995;**39**:671–7. 1996040117.
- Virgilio 1979** *{published data only}*  
Virgilio RW, Rice CL, Smith DE, et al. Crystalloid vs. colloid resuscitation: is one better? A randomized clinical study. *Surgery* 1979;**85**(2):129–39. 1979118289.
- Woittiez 1998** *{unpublished data only}*  
Timmer B, Hondebrink Y, Oude Nijhuis J, Woittiez AJJ. Restoration of colloid osmotic pressure in hypoalbuminaemic patients. *Netherlands Journal of Medicine* 1998;**52**:A42.  
  
Woittiez AJ. Restoration of colloid osmotic pressure in post operative intensive care patients. A randomised placebo controlled trial with albumin 20% and hydroxy-ethyl starch. In: Medical Editors' Trial Amnesty. In: The Cochrane Controlled Trials Register In: The Cochrane Library, Issue 2, 1998. Oxford: Update Software.
- Wojtysiak 1992** *{published data only}*  
Binkley JF, Brown RO, Wojtysiak SL, Powers DA, Kudsk KA. Effects of human albumin administration on visceral protein markers in patients receiving parenteral nutrition. *Clinical Pharmacy* 1993;**Vol 12**:377–379.  
  
Wojtysiak SL, Brown RO, Roberson D, Powers DA, Kudsk KA. Effect of hypoalbuminaemia and parenteral nutrition on free water excretion and electrolyte-free water resorption. *Critical Care Medicine* 1992;**20**:164–9. 1992146052.
- Woods 1993** *{published data only}*  
Woods MS, Kelley H. Oncotic pressure, albumin and ileus: the effect of albumin replacement on postoperative ileus. *The American Surgeon* 1993;**59**:758–63. 1994057741.
- Zetterstrom 1981a** *{published data only}*  
Zetterstrom H, Hedstrand U. Albumin treatment following major surgery. I. Effects on plasma oncotic pressure, renal function and peripheral oedema. *Acta Anaesthesiologica Scandinavica* 1981;**25**:125–32. 1982109921.
- Zetterstrom 1981b** *{published data only}*  
Zetterstrom H. Albumin treatment following major surgery. II. Effects on postoperative lung function and circulatory adaptation. *Acta Anaesthesiologica Scandinavica* 1981;**25**:133–41. 1982109922.

## References to studies excluded from this review

### Artru 1989

Artru F, Philippon B, Flachaire E, et al. A controlled study of Dextran 40: effect on cerebral blood flow and metabolic rates in acute head trauma. *Intensive Care Medicine* 1989;**15**(8):499–504.

### Brehme 1993

Brehme S, Keysser G, Turowski A, Schmidt HH. Hemorheologic effects of hydroxyethyl starch 200/0.5, dextran 40, oxypolygelatine and full electrolyte solution over 48 hours. *Z Gesamte Inn Med* 1993;**48**(10):506–10.

### Carlson 1979

Carlson GC, Kahn RC, Bertoni G, Campfield PB, Howland WS, Goldiner PL. Rapid volume expansion in patients with interstitial lung diseases. *Anesthesia and Analgesia* 1979;**58**:13–8.

### Fiorica 1991

Fiorica JV, Roberts WS, Hoffman MS, Barton DP, Finan MA, Lyman G, Cavanagh D. Concentrated albumin infusion as an aid to postoperative recovery after pelvic exenteration. *Gynecologic Oncology* 1991;**43**:265–9.

### Goslinga 1992

Goslinga H, Eijzenbach V, Heuvelmans JH, van de Nes JC, Kurk RM, Bezemer PD. Individualized hemodilution in acute brain infarct using a 20% albumin solution and physiological saline solution. *Ned Tijdschr Geneesk* 1992;**136**(49):2422–8.

Goslinga H, Eijzenbach V, Heuvelmans JH, et al. Custom-tailored hemodilution with albumin and crystalloids in acute ischemic stroke. *Stroke* 1992;**23**(2):181–8.

Goslinga H, Heuvelmans JH, Schmid Schonbein H. Hemodilution and rehydration in acute ischemic stroke. A preliminary report on the Amsterdam Stroke Study. *Acta Medica Austriaca* 1991;**18** Suppl 1:41–4.

### Grundmann 1985

Grundmann R, Heistermann S. Postoperative albumin infusion therapy based on colloid osmotic pressure. *Archives of Surgery* 1985;**120**:911–5.

### Grundmann 1986

Grundmann R, von Lehndorff C. Indications for postoperative human albumin therapy in the intensive care unit: a prospective randomised study. *Langenbecks Archiv fur Chirurgie* 1986;**367**:235–46.

**Hauser 1980**

Hauser CJ, Shoemaker WC, Turpin I, Goldberg SJ. Oxygen transport responds to colloids and crystalloids in critically ill surgical patients. *Surgery* 1980;**150**(6):811–6.

**Lagonidis 1995**

Lagonidis D, Magder S. Acute volume loading with colloid vs. crystalloid after coronary artery bypass. *Intensive Care Medicine* 1992;**18**:(suppl 2):S225.

**Lennihan 2000**

Lennihan L, Mayer SA, Fink ME, Beckford A, Paik MC, Zhang H, Wu Y, Kledanoff LM, Raps EC, Solomon RA. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage. *Stroke* 2000;**31**(2):383–91.

**Magder 1999**

Magder S, Lagonidis D. Effectiveness of albumin versus normal saline as a test of volume responsiveness in post-cardiac surgery patients. *Journal of Critical Care* 1999;**14**(4):164–171.

**Martin 1999**

Martin GS, Mangialardi RJ, Wheeler AP, Berhard GR. Albumin and diuretics in acute lung injury/acute respiratory distress syndrome. *American Journal of Respiratory Critical Care Medicine* 1999;**159**(3):A376.

**Metildi 1984**

Metildi LA, Shackford SR, Virgilio RW, Peters RM. Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency. *Surgical Gynecology and Obstetrics* 1984;**158**(3):207–12.

**Steinberg 1989**

Steinberg B, Kochs E, Bause H, Schulte am Esch J. Effects of low molecular weight hydroxyethyl starch (HES 40) in comparison with Ringer solution on oxygen tension in skeletal muscles of infected patients. *Anesthesie Intensivtherapie Notfallmedizin* 1989;**24**(6):377–81.

**Tomita 1994**

Tomita H, Ito U, Tone O, Masaoka H, Tominaga B. High colloid oncotic therapy for contusional brain edema. *Acta Neurochirurgica* 1994;**suppl**:547–549.

**References to studies awaiting assessment****Lundstrom 2000****References to ongoing studies****Martin**

Martin G. Bioimpedance measures of albumin effects in acute lung injury.

**Additional references****ABPI 1998**

*ABPI Compendium of data sheets and summaries of produce characteristics 1998-99*. Association of the British Pharmaceutical Industry, London 1998.

**Egger 1997**

Egger M, Minder CE, Schneider M, Davey Smith G. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–634.

**Fleck 1985**

Fleck A, Raines G, Hawker F, Trotter J, Wallace P, Ledingham I, Calman KC. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. *Lancet* 1985;**I**:781–4.

**Goldwasser 1997**

Goldwasser P, Feldman J. Association of serum albumin and mortality risk. *Journal of Clinical Epidemiology* 1997;**50**(6):693–703.

**McClelland 1990**

McClelland DB. Human albumin solutions. *BMJ* 1990;**300**:35–7.

**Oxman 1994**

Oxman A, Cook D, Guyatt GH for the Evidence-based Medicine Working Group. User's Guides to the Medical Literature. VI. How to use an overview. *Journal of the American Medical Association* 1994;**272**:1367–71.

**Schulz 1996**

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association* 1995;**273**(5):408–12.

**Soni 1995**

Soni N. Wonderful albumin?. *BMJ* 1995;**310**:887–8.

**References to other published versions of this review****CIGAR 1998**

The Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;**317**:235–40.

\* Indicates the major publication for the study

**T A B L E S****Characteristics of included studies**

Study	Bland 1973
Methods	Randomised controlled trial. Therapy cards were randomised in pairs matched for weight. Method of allocation concealment not fully described.

### Characteristics of included studies (Continued)

Participants	Newborn infants considered at high risk for developing respiratory distress. Those with a cord serum protein level less than 4.6g/100ml and at least one of the following; birthweight less than 2500g, gestational age less than 37 weeks, arterial pH less than 7.25.
Interventions	1) Intervention (n=50) received 8ml/kg 25% salt poor albumin. 2) Control group (n=50) received 8ml/kg 5% dextrose in water.
Outcomes	Deaths reported within 28 days.
Notes	
Allocation concealment	B

#### Study **Bland 1976**

Methods	Randomised controlled trial. Method of allocation concealment not fully described.
Participants	Premature infants (less than 37 weeks gestation), with hypoproteinaemia (cord serum total protein of 4.6g/100ml or less).
Interventions	1) Intervention group (n=14) received 8ml/kg salt-poor albumin. 2) Comparison group (n=13) received 8ml/kg glucose in water.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	B

#### Study **Boldt 1993**

Methods	Randomised controlled trial. Method of allocation concealment not described in published report. Authors were contacted and confirmed the use of sealed opaque envelopes.
Participants	Men undergoing elective aortocoronary bypass grafting, who had a pulmonary capillary wedge pressure of less than 5mmHg after induction of anaesthesia.
Interventions	1) Intervention (n=15): Albumin 5%. 2) Control (n=15): No additional volume.
Outcomes	Deaths not reported. Authors were contacted and confirmed that there were no deaths in the albumin nor the control group.
Notes	Follow-up to 1 day.
Allocation concealment	A

#### Study **Boutros 1979**

Methods	Randomised controlled trial. Method of allocation concealment not fully described.
Participants	Participants were undergoing major operative procedures on the abdominal aorta.
Interventions	1) Intervention group (n=7) received albumin in 5% dextrose 2) Control group (n=17) received 5% dextrose in lactated Ringers and 5% dextrose in 0.45 NaCl . Allocated fluids were used on admission to ICU, following surgery.
Outcomes	Deaths reported.
Notes	Follow-up to 48 hours after the end of the operation.
Allocation concealment	B

#### Study **Brown 1988**

Methods	Randomised controlled trial. Patients entered into the study were assigned to one of two treatment groups by a table of random numbers. Method of allocation concealment not described. Author contacted - no allocation concealment.
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### Characteristics of included studies (Continued)

Participants	All patients who required central TPN and had hypoalbuminaemia (serum albumin concentration below 3.0g/dl). Patients who were thermally injured, had nephrotic syndrome or required protein restriction were excluded.
Interventions	1) The intervention group received central TPN plus normal serum albumin (n=33). 2) The control group (n=34) received central TPN alone.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	C

#### Study Ernest 1999

Methods	Randomised controlled trial, not blinded.
Participants	18 septic, critically ill patients where a fluid infusion was clinically indicated.
Interventions	1) 5% albumin (n=9) 2) normal saline (n=9)
Outcomes	Information on death not collected.
Notes	Follow up for about an hour after infusion
Allocation concealment	C

#### Study Ernest 2001

Methods	Randomised controlled trial, not blinded
Participants	40 postoperative cardiac surgical patients.
Interventions	1) 5% albumin (n=23) 2) normal saline (n=17)
Outcomes	Information on death not collected.
Notes	Follow up for 40 minutes after infusion. Trial conducted in 1992.
Allocation concealment	C

#### Study Foley 1990

Methods	Patients were randomly assigned to either a treatment or non-treatment group by medical record number.
Participants	Hypoalbuminaemic (serum albumin <25g/L) critically ill patients. Potential subjects with Child's class C cirrhosis were excluded.
Interventions	1) The treatment group (n=18) received 25-50g per day of 25% albumin in addition to full nutritional support with parenteral nutrition. Albumin administration was continued daily until serum albumin levels exceeded 25 g/L after which patients received additional albumin as needed to keep the albumin level at 25 g/L or higher. 2) The non treatment group (n=22) received no exogenous concentrated albumin.
Outcomes	Deaths reported.
Notes	Follow up to discharge.
Allocation concealment	C

#### Study Gallagher 1985

Methods	Randomised controlled trial. Method of allocation concealment not described. Author contacted - allocation concealment by computerised system - patient details were entered before treatment assignment was revealed.
Participants	Patients after coronary artery bypass graft surgery.
Interventions	1) Treatment group received 5% albumin (n=5)

**Characteristics of included studies (Continued)**

	2) The control group received lactated Ringers (n=5).
Outcomes	Deaths were not reported. Author contacted and confirmed that there were no deaths in either group.
Notes	Follow-up to 1 day.
Allocation concealment	A

<b>Study</b>	<b>Golub 1994</b>
Methods	Computer randomisation - method of allocation concealment not described. Author contacted and confirmed that allocation concealment was by the use of sealed opaque envelopes.
Participants	Patients in the surgical intensive care unit of a community hospital with circulating albumin concentrations of <3.0g/dL.
Interventions	1) The treatment group (n=116) received 37.5g/day of albumin until the circulating albumin concentration increased to 3.0g/dL. 2) The control group received no supplemental albumin. Both groups received standard nutritional support.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	A

<b>Study</b>	<b>Goodwin 1983</b>
Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	79 thermally injured patients. No other inclusion criteria were reported. All of the participants were previously healthy young adults.
Interventions	1) The treatment group (n=40) group received 2.5% albumin in Ringer's lactate 2) The control group (n=39) Ringers lactate. Allocated fluid was used throughout resuscitation.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	B

<b>Study</b>	<b>Greenhalgh 1995</b>
Methods	Method of random allocation not described. Author contacted and confirmed the use of a randomisation scheme controlled by the pharmacy.
Participants	Patients aged 18 years or younger with acute burns.
Interventions	1) High albumin group (n=34): Patients were supplemented with human albumin to maintain serum levels between 2.5 and 3.5g/dL. Albumin was supplied as a continuous drip of 25% human albumin at a rate of 3-10mL/hour. Supplementation was discontinued if serum albumin levels remained >2.5 g/dL without supplementation or if intravenous support was discontinued. 2) Low albumin group (n=36): Patients were not given albumin supplementation unless levels dropped <1.5 g/dL. During burn shock, patients were allowed to receive albumin if they had levels <2.0 g/dL and were receiving >4 mL/Kg/% burn fluid resuscitation.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	A

<b>Study</b>	<b>Greenough 1993</b>
Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.

### Characteristics of included studies (Continued)

Participants	Infants between 24 and 34 weeks gestational age, who were ventilator dependent, and had a serum albumin level of less than or equal to 30g/l.
Interventions	1) Intervention group (n=20) received 5ml/kg 20% salt-poor human albumin. 2) Control group (n=20) received 5ml/kg of the infant's maintenance fluids.
Outcomes	Deaths were not reported. Author contacted and provided data on deaths.
Notes	Follow-up to 24 hours after infusion.
Allocation concealment	A

#### Study Grundmann 1982

Methods	Randomised controlled trial. Method of allocation concealment not fully described.
Participants	Participants were undergoing partial gastrectomy. The average age was 50 years (range 19-84).
Interventions	1) Intervention group (n=14) group received human albumin 2) Control group (n=6) details of crystalloid were not reported. Allocated fluid was continued for 4 days after operation.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	B

#### Study Jelenko 1978

Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Participants had burns covering more than 20% of body surface.
Interventions	1) Intervention group (n=7) received albumin in hypertonic saline (240MeQ Na+, 120 MeQ Chloride, 120 MeQ lactate, 3.5torr/liter); 2) Control group (n=7) received hypertonic saline (240MeQ Na+, 120 MeQ Chloride, 120 MeQ lactate). Allocated fluid was used to the end of resuscitation.
Outcomes	Deaths reported.
Notes	Follow-up to 5 days.
Allocation concealment	B

#### Study Kanarek 1992

Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.
Participants	Sick premature newborn infants whose serum albumin was less than 3g/dL
Interventions	1) Intervention group (n=12) received TPN with added albumin. 2) Control group (n=12) received no added albumin.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	A

#### Study Lowe 1977

Methods	Randomised controlled trial. The solutions were randomised by opening a sealed envelope containing a card denoting the appropriate fluid.
Participants	Participants were undergoing emergency laparotomy for acute abdominal trauma.
Interventions	1) Intervention group (n=57) received 50g albumin in 200ml in Ringers lactate;

**Characteristics of included studies (Continued)**

	2) Crystalloid group (n=84) received Ringer's lactate. Allocated fluid was used throughout the pre- and intra-operative period.
Outcomes	Deaths reported.
Notes	Follow-up to 5 days post-operatively. Data on the 30 participants with chest injuries who were left out of the Lowe 1977 report, but included in Moss 1981, have been included in the meta-analysis.
Allocation concealment	A

**Study Lucas 1978**

Methods	Randomised controlled trial. Randomisation was based on the last digit of each patient's case number.
Participants	52 seriously injured patients.
Interventions	1) Intervention group (n=27) received supplemental salt-poor albumin totalling a maximum of 150g during operation and 150g per day over the next five days. 2) Control group (n=25) received standard resuscitation regimen but no supplemental albumin.
Outcomes	Deaths reported.
Notes	In the final report of 94 randomised patients deaths were not reported. However, in this preliminary report of 52 injured patients deaths were reported.
Allocation concealment	C

**Study McNulty 1993**

Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Patients following elective cardiopulmonary bypass.
Interventions	1) Intervention group (n=14) received 5% albumin. 2) Control group (n=14) received isotonic crystalloid.
Outcomes	Deaths not reported.
Notes	Length of follow-up unspecified.
Allocation concealment	B

**Study Nielsen 1985**

Methods	Randomized controlled trial. Method of allocation concealment not described.
Participants	Patients admitted for reconstructive surgery of the abdominal aorta. Twenty six patients were randomised.
Interventions	1) Intervention (n=13): 80 g of albumin administered in units of 100 ml 20% human serum albumin on the day of the operation and 20 g albumin daily on the following three postoperative days. 2) Control group (n=13): no supplemental albumin.
Outcomes	Deaths not reported. Author when contacted confirmed that there were no deaths in either group.
Notes	Follow-up 4 days.
Allocation concealment	B

**Study Nilsson 1980**

Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.
Participants	Patients with colorectal cancer undergoing elective surgery with resection of the tumour and primary anastomosis.
Interventions	1) Intervention group (n=29) received 20-25g per day of albumin (as 5% albumin or 20% albumin) for three days, starting on the day after the operation. 2) Control group (n=30) received no albumin.
Outcomes	Deaths reported.

### Characteristics of included studies (Continued)

Notes	Follow up to discharge.
Allocation concealment	A
<b>Study</b>	<b>Oca 1999</b>
Methods	Randomised controlled trial. Allocation concealment was by the use of sealed opaque sequentially numbered envelopes. Information obtained on contact with the author.
Participants	24 neonates being treated for hypotension. Hypotension was defined as an oscilometric mean arterial blood pressure <30 mmHg for at least 30 minutes. Exclusion criteria consisted of proven sepsis, life-threatening congenital abnormalities, congenital hear disease, unresolved thoracic air leak, insulin-requiring maternal diabetes mellitus or treatment with high-frequency ventilation.
Interventions	1) 5% albumin (n=11) 2) normal saline (n=13)
Outcomes	Mean arterial blood pressure.
Notes	Follow-up to discharge
Allocation concealment	A
<b>Study</b>	<b>Pockaj 1994</b>
Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Participants required fluid resuscitation as a result of vascular leak syndrome associated with Interleukin-2 therapy for metastatic cancer.
Interventions	1) Intervention group (n=54) received 5% albumin n 154meq/L NaCl; 2) Control group (n=53) received 0.9% normal saline with 154Meq/L NaCl.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	B
<b>Study</b>	<b>Prien 1990</b>
Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Patients undergoing hemipancreato-duodenectomy (Whipple's operation).
Interventions	1) Intervention group (n=6) received 20% human albumin to maintain central venous pressure at the pre-operative level. 2) Control group (n=6) received Ringer's lactate.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	B
<b>Study</b>	<b>Rackow 1983</b>
Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Participants were above 18 years of age, and had any one of the following pre-determined indicators of shock: systolic blood pressure of 90mmHg or less, a cardiac index of less than 2.2L./min.m2, a serum arterial lactate greater than 18mg/dl and WP less than 15mmHg.
Interventions	1) Intervention group ( n= 9) received 5% albumin 2) Control group (n=8) received 0.9% NaCl. Allocated fluid was given as needed until the end of resuscitation.
Outcomes	Deaths reported.

### Characteristics of included studies (Continued)

Notes	Follow-up to discharge.
Allocation concealment	B
<b>Study</b>	<b>Rubin 1997</b>
Methods	Patients were randomised using “a closed envelope system in the pharmacy”.
Participants	Patients with hypoalbuminaemia (<2.5g/dL) who required TPN for at least six days, were not pregnant or under age, and did not have metastatic cancer, cirrhosis, or nephrotic syndrome.
Interventions	1) Intervention group (n=16) 25g on normal serum albumin 2) Control group (n=15) 100 mL of normal saline placebo over a 1 hour period daily.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	A
<b>Study</b>	<b>SAFE 2004</b>
Methods	Central randomisation accessed on the internet through a secure website with use of a minimisation algorithm. Blinding was assured through the use of specially designed masking cartons and specially designed and manufactured administration sets. The authors report that the effectiveness of the blinding was confirmed in a formal study before the trial was initiated.
Participants	Patients 18 years of age or older admitted to ICU who the treating clinician judged to require fluid administration to maintain or increase intravascular volume, with this decision supported by the fulfillment of at least one objective criterion. Patients admitted after cardiac surgery, after liver transplantation, or for the treatment of burns were excluded.
Interventions	1) 4% Albumin or 2) Normal saline  The allocated study treatment was used for all fluid resuscitation in the ICU until death or discharge or until 28 days after randomisation. The treating clinicians determined the amount and rate of fluid administration according to each patient’s clinical status and response to treatment.
Outcomes	Deaths reported
Notes	28 day mortality
Allocation concealment	A
<b>Study</b>	<b>Shah 1977</b>
Methods	Randomised controlled trial. allocation by sealed envelope.
Participants	Patients with severe, multiple trauma and a systolic blood pressure of less than 90mmHg. All patients were adults and both sexes were included.
Interventions	1) Intervention group (n=9) 5% salt-poor albumin in Ringers lactate 2) Control group (n=11) Ringer’s lactate for resuscitation, volume infused guided by physiological parameters.
Outcomes	Death reported.
Notes	Length of follow-up not stated.
Allocation concealment	A
<b>Study</b>	<b>Skillman 1975</b>
Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Participants were undergoing elective abdominal reconstructive surgery.
Interventions	1) Intervention group received 25% concentrated salt-poor albumin and 5% albumin in saline.

**Characteristics of included studies (Continued)**

2) Control group received Ringer's lactate with 5% dextrose. Allocated fluid was given intra-operatively. All patients received crystalloids only for pre-loading before surgery.

Outcomes	Deaths were not reported. Author could not be contacted.
Notes	Follow-up to 1 day.
Allocation concealment	B

**Study So 1997**

Methods	Randomised controlled trial. Method of allocation concealment not described. Author contacted and confirmed that allocation concealment was by computer randomisation. Details of patient were entered before group allocation revealed.
Participants	Pre-term infants weighing 540 to 1959g at birth, with gestational ages of 23 to 34 weeks, who developed hypotension within the first two hours of life.
Interventions	1) Intervention group (n=32) were given 5% albumin at a dose of 10mg/Kg by slow intravenous infusion over 30 minutes. 2) Control group (n=31) were given 0.9%NaCl at a dose of 10mg/kg by slow intravenous infusion over 30 minutes.
Outcomes	Deaths reported.
Notes	Follow up to discharge.
Allocation concealment	A

**Study Tollofsrud 1995**

Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.
Participants	Patients undergoing elective coronary artery bypass surgery. Patients with left ventricular ejection fraction less than 40%, valvular heart disease, ventricular aneurysm, arrhythmia, diabetes mellitus, renal failure or lung disease were excluded.
Interventions	1) Intervention group (n=10) received albumin 40mg/ml whenever fluid was required to stabilise haemodynamics. 2) Control group (n=10) received Ringers acetate.
Outcomes	Deaths reported.
Notes	Follow-up to 48 hours.
Allocation concealment	A

**Study Virgilio 1979**

Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Participants were undergoing abdominal aortic surgery.
Interventions	1) Intervention group (n=15) received 5% albumin in Ringer's lactate 2) Control group (n=14) received Ringers lactate. Allocated fluid was used during operation for maintenance of pre-defined physiological parameters, and the resuscitation was continued with the allocated fluid until the day following the operation. This was followed by 5% dextrose in half-normal saline, with potassium chloride as needed.
Outcomes	Deaths reported.
Notes	Follow-up 2 and a half weeks.
Allocation concealment	B

### Characteristics of included studies (Continued)

<b>Study</b>	<b>Woittiez 1998</b>
Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.
Participants	Post-operative intensive care patients.
Interventions	1) Intervention group (n=15) received 20% albumin. 2) Control group (n=16) received 0.9% NaCl.
Outcomes	Unpublished data on deaths were provided by the trialist.
Notes	Length of follow-up unspecified.
Allocation concealment	A

<b>Study</b>	<b>Wojtysiak 1992</b>
Methods	Randomised controlled trial. Table of random numbers was used to generate the random sequence. Method of allocation concealment not described in published report. The author was contacted and indicated that there was inadequate allocation concealment.
Participants	Patients between the ages of 18 and 75 years who were to receive parenteral nutrition and had a serum albumin concentration <3.0 g/dL. Patients were excluded if they had renal impairment, liver impairment or were haemodynamically unstable.
Interventions	1) Intervention group (n= 15) had 25g of human albumin added to each litre of parenteral nutrition. 2) Control group (n=15) had no supplemental albumin.
Outcomes	Deaths not reported in published report. Author when contacted confirmed that there were no deaths in either group.
Notes	Follow-up to 5 days.
Allocation concealment	C

<b>Study</b>	<b>Woods 1993</b>
Methods	Randomised controlled trial. Patients with even hospital numbers were randomised to the group receiving albumin while those patients with odd hospital numbers were randomised to the group not receiving supplemental albumin.
Participants	Patients undergoing surgery for abdominal aortic aneurysm, aortoiliac or aortofemoral bypass.
Interventions	1) Intervention group (n=37): albumin was replaced to a level greater than or equal to 3.5 g/dL. 2) Control group (n=32): received no supplemental albumin.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	C

<b>Study</b>	<b>Zetterstrom 1981a</b>
Methods	The patients were randomly divided into two groups. The method of allocation concealment is not described. Author was contacted and confirmed the use of sealed opaque envelopes.
Participants	Adult patients undergoing elective major abdominal surgery.
Interventions	1) Intervention group (n=15) 2) Control group (n=15) A similar schedule of fluid therapy and blood replacement was followed in the intervention and control groups. However, the albumin group received a 20% solution of human albumin intravenously according to the following scheme: At the end of the operation: 100ml. Postoperatively on the day of the operation: 200-300 ml.

### Characteristics of included studies (Continued)

	First day after the operation: 200 ml. Following 3 days 100 ml each day.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	A

Study	Zetterstrom 1981b
Methods	Patients were randomly divided into two groups. Method of allocation concealment was not described. Author was contacted and confirmed the use of sealed opaque envelopes.
Participants	Patients undergoing elective reconstruction of the abdominal aorta.
Interventions	1) Intervention group (n=9) 2) Control group (n=9) Postoperatively, the aim of fluid administration was to keep the pulmonary arterial occlusion pressure equal to the preoperative level. When lower values were recorded, the patients in the control group were given a balanced electrolyte solution of the Ringer type, whereas the albumin patients received a 5% solution of human albumin.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	A

### Characteristics of excluded studies

Artru 1989	Intervention to control intracranial pressure not directed at fluid resuscitation.
Brehme 1993	Intervention directed at haemodilution, not at volume replacement.
Carlson 1979	Randomised controlled trial of pre-operative volume expansion during anaesthesia.
Fiorica 1991	Not a randomised trial. The first 18 patients received standard maintenance crystalloid solution. The next 10 consecutive patients received 100g of a concentrated 25% albumin solution.
Goslinga 1992	Intervention directed at haemodilution, not volume replacement.
Grundmann 1985	This was a randomised controlled trial of 220 patients, 106 were given albumin when their colloid osmotic pressure (COP) fell below 24 cm water and 114 were given albumin when their COP fell below 29 cm water. Patients were not randomised to albumin or no albumin, nor were they randomised to supplemental albumin versus normal amounts of albumin, rather, this was a trial of different criteria for albumin supplementation. It is unlikely therefore that the two arms of the trial were comparable and hence the trial is excluded.
Grundmann 1986	This was a randomised controlled trial to examine whether postoperative human albumin supply is justified in intensive care patients in the case that the colloid osmotic pressure decreases below 26 centimetres of water. The therapy group received human albumin only if the colloid osmotic pressure dropped below 26 cm water. The control group also received albumin but only for resuscitation of cardiac output and central venous pressure. The trial was excluded because both intervention and control groups received albumin.
Hauser 1980	Cross-over trial.
Lagonidis 1995	Intervention was pre-loading for coronary artery bypass surgery.
Lennihan 2000	Participants had suffered subarachnoid hemorrhage and therefore did not meet the inclusion criteria.
Magder 1999	Participants were stable patients following cardiopulmonary bypass surgery and therefore did not meet the inclusion criteria.
Martin 1999	Intervention involved comparison of albumin with furosemide versus placebo therefore did not meet the inclusion criteria.

### Characteristics of excluded studies (Continued)

Metildi 1984	Participants were admissions to an intensive care and a trauma unit with adult respiratory distress syndrome and established pulmonary failure. Included both trauma and non-trauma patients and therefore did not meet the inclusion criteria for the review.
Steinberg 1989	Cross-over trial.
Tomita 1994	Randomised controlled trial of normal versus high oncotic pressure following head injury. Patients were not randomised to albumin or no albumin. Albumin and furosemide were used together to achieve high oncotic pressure.

### Characteristics of ongoing studies

Study	Martin
Trial name or title	Bioimpedance measures of albumin effects in ALI.
Participants	Hypoproteinemic patients with ALI or ARDS (total projected n=40, current n=24).
Interventions	Patients randomised to continuous infusion furosemide with or without blinded administration of albumin (25g of 25% albumin) for 3 days.
Outcomes	Powered for physiology (changes in weight, serum chemistries, oxygenation, hemodynamics) with additional outcome data (ventilator free days, ICU free days, organ failure, hospital LOS, mortality) to 28 days or hospital discharge (whichever is greater).
Starting date	
Contact information	Greg S Martin, M.D Pulmonary & Critical Care Medicine 80 Butler Steet , SE Grady Memorial Hospital, Suite 2D-004 Atlanta, GA 30335 USA Greg_Martin@emoryhealthcare.org
Notes	

## ANALYSES

### Comparison 01. supplemental albumin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 deaths	32	8452	Relative Risk (Fixed) 95% CI	1.04 [0.95, 1.13]

## INDEX TERMS

### Medical Subject Headings (MeSH)

Blood Proteins [\*therapeutic use]; Critical Illness [mortality; \*therapy]; Fluid Therapy; Plasma Substitutes [\*therapeutic use]; Randomized Controlled Trials; Serum Albumin [\*therapeutic use]

### MeSH check words

Humans

## COVER SHEET

**Title** Human albumin solution for resuscitation and volume expansion in critically ill patients

**Human albumin solution for resuscitation and volume expansion in critically ill patients (Review)**  
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<b>Authors</b>	The Albumin Reviewers (Alderson P, Bunn F, Li Wan Po A, Li L, Roberts I, Schierhout G)
<b>Contribution of author(s)</b>	Phil Alderson (UK Cochrane Centre) searched The Cochrane Central Register of Controlled Trials for relevant trials, extracted the data from the trials, and commented on the paper; Frances Bunn (London School of Hygiene & Tropical Medicine) searched the Cochrane Injuries Group Specialised Register for relevant trials, obtained copies of relevant papers, wrote to authors for further information on allocation concealment, and commented on the paper; Carol Lefebvre (UK Cochrane Centre) designed the search strategies for The Cochrane Central Register of Controlled Trials and EMBASE, and searched these two databases for relevant trials; Leah Li (Institute of Child Health) did the funnel plot and the regression test of funnel plot asymmetry; Alain Li Wan Po (Centre for Evidence-Based Pharmacotherapy, University of Nottingham) helped to write the paper; Ian Roberts (London School of Hygiene & Tropical Medicine) designed the protocol, extracted data from the trials, contacted authors for unpublished data, and wrote the paper; Gillian Schierhout proposed the study hypothesis, and conducted preliminary searches of MEDLINE, EMBASE, and BIDS Index to Scientific and Technical Proceedings.
<b>Issue protocol first published</b>	1998/3
<b>Review first published</b>	1998/3
<b>Date of most recent amendment</b>	15 November 2005
<b>Date of most recent SUBSTANTIVE amendment</b>	20 August 2004
<b>What's New</b>	<p>August 2004 One new trial has been included (SAFE 2004) with the analysis, results and discussion amended accordingly.</p> <p>February 2002 An updated search for new trials was done in September 2002. One trial was found meeting the inclusion criteria but did not record data on mortality (Ernest 2001). Since the review was first published several new randomised control trials have been initiated. Details of these trials are given in the ongoing trials section.</p>
<b>Date new studies sought but none found</b>	Information not supplied by author
<b>Date new studies found but not yet included/excluded</b>	Information not supplied by author
<b>Date new studies found and included/excluded</b>	01 September 2002
<b>Date authors' conclusions section amended</b>	Information not supplied by author
<b>Contact address</b>	<p>Prof Ian Roberts  Professor of Epidemiology &amp; Public Health  Nutrition &amp; Public Health Intervention Research Unit  London School of Hygiene &amp; Tropical Medicine  North Courtyard  Keppel Street  London  WC1E 7HT  UK  E-mail: Ian.Roberts@lshtm.ac.uk  Tel: +44 020 7958 8128  Fax: +44 020 7299 4663</p>
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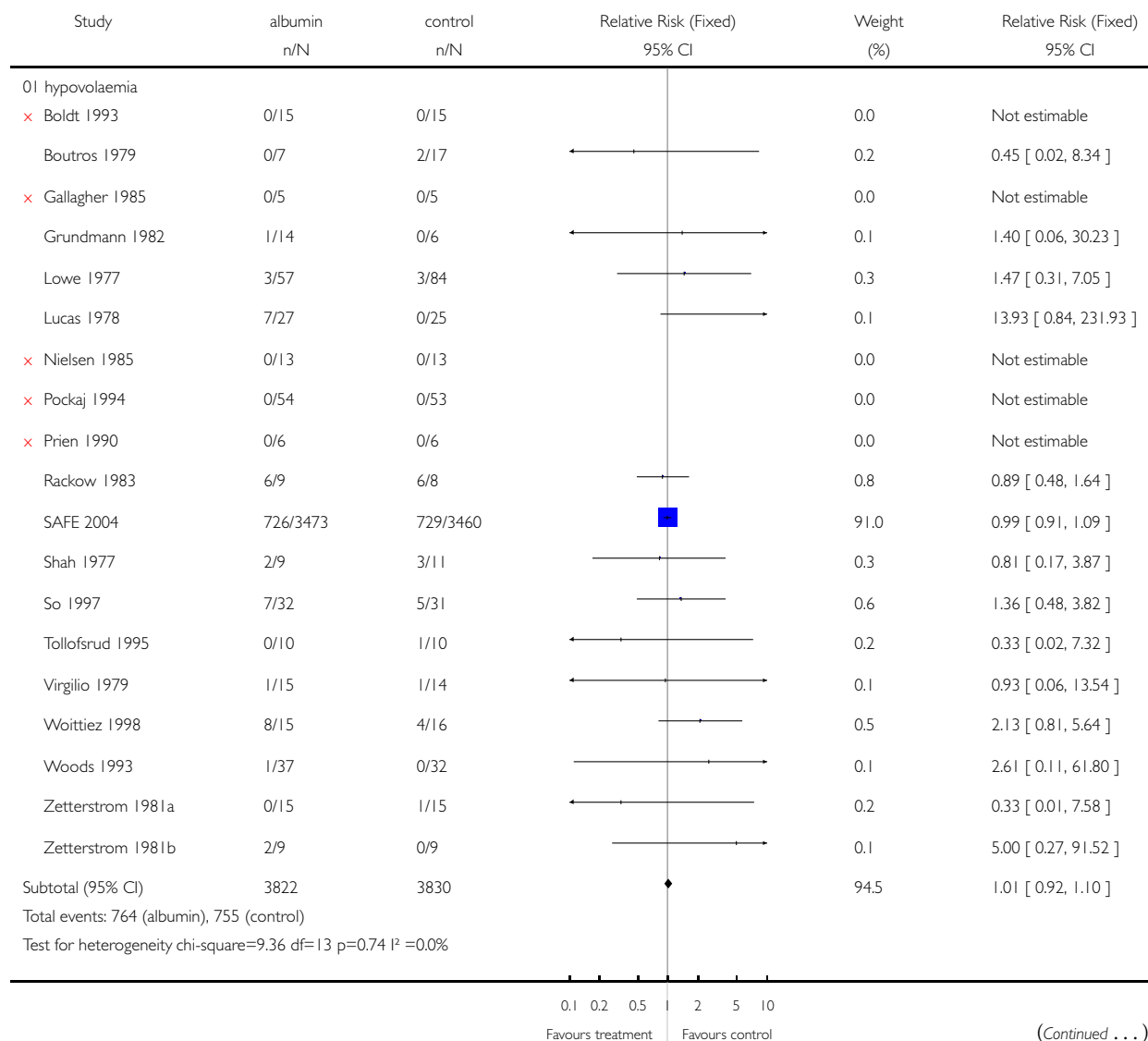
**GRAPHS AND OTHER TABLES**

**Analysis 01.01. Comparison 01 supplemental albumin, Outcome 01 deaths**

Review: Human albumin solution for resuscitation and volume expansion in critically ill patients

Comparison: 01 supplemental albumin

Outcome: 01 deaths



(... Continued)

