Perioperative fluid volume optimization following proximal femoral fracture (Review)

Brammar A, Nicholson A, Trivella M, Smith AF

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TABLE OF CONTENTS

[Intervention Review]

Perioperative fluid volume optimization following proximal femoral fracture

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ABSTRACT

Background

Proximal femoral fracture (PFF) is a common orthopaedic emergency, affecting mainly elderly people at high risk of complications. Advanced methods for managing fluid therapy during treatment for PFF are available, but their role in reducing risk is unclear.

Objectives

To compare the safety and effectiveness of different methods of perioperative fluid optimization in adult participants undergoing surgical repair of hip fracture. We considered the following methods: advanced invasive haemodynamic monitoring, such as transoesophageal Doppler and pulse contour analysis; a protocol using standard measures, such as blood pressure, urine output and central venous pressure; and usual care.

Comparisons of fluid types (e.g. crystalloid vs colloid) and other methods of optimizing oxygen delivery, such as blood product therapies and pharmacological treatment with inotropes and vasoactive drugs, are considered elsewhere.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 9*);* MEDLINE (1966 to October 2012); and EMBASE (1980 to October 2012) without language restrictions. We ran forward and backward citation searches on identified trials. We contacted authors and searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform for unpublished trials. This is an updated version of a review published in 2004. The original search was performed in October 2003.

Selection criteria

We included randomized controlled trials (RCTs) in adult participants undergoing surgical treatment for PFF, which compared any two of advanced haemodynamic monitoring, protocols using standard measures or usual care, irrespective of blinding, language or publication status.

Data collection and analysis

Two review authors assessed the impact of fluid optimization interventions on outcomes of mortality, length of hospital stay, return of participant to pre-fracture accommodation and mobility at six months and adverse events in hospital. We pooled data using risk ratio or mean difference for dichotomous or continuous data, respectively, based on random-effects models.

Main results

We included three RCTs with a total of 200 participants. One of these included studies was found to have a high risk of bias; no trial featured all pre-specified outcomes. We found one trial for which data are awaited for classification and two ongoing trials. One included study with low risk of bias found that compared with usual care, time to medical fitness for discharge was shorter with the use of advanced haemodynamic monitoring (mean reduction 6.20 days, 95% CI 2.3 to 10.1 days; 59 participants, one trial) and with the use of protocols that apply standard measures (mean reduction 3.9 days, 95% CI 0.75 to 7.05; 57 participants, one trial). Our results are consistent with both increased and decreased risk of mortality and adverse events in participants receiving the intervention. No data for other outcomes were available. Our results are limited by the quantity of available data.

Authors' conclusions

Three studies considering a total of 200 participants reveal an absence of evidence that fluid optimization strategies improve outcomes for participants undergoing surgery for PFF. Length of hospital stay may be improved, but lack of good quality data leaves uncertainty. Further research powered to test some of these outcomes is ongoing.

PLAIN LANGUAGE SUMMARY

Optimization of fluid levels in people suffering hip fractures

Hip fractures are common in elderly people, who often have medical conditions that put them at risk of developing other problems whilst their fracture is treated. Treatment usually involves an operation to fix the break in the bone, and it is possible that giving too much or too little fluid to a patient around this time may increase the risk of further problems. Healthcare staff can use many approaches in trying to determine how much fluid a patient needs in this situation, but it is not clear if some methods are better than others. For this Cochrane review, researchers from The Cochrane Collaboration looked at research on the effects of different methods of optimizing fluid levels for adult men and women who underwent surgery for any type of hip fracture. We searched the databases to October 2012 and identified three studies (randomized controlled trials) with a total of 200 people, each of which compared two or three methods of guiding fluid therapy. These methods include 'usual care' (where staff use changes in basic measurements, such as heart rate, to decide for themselves how much fluid to give), 'protocols using standard measures' (where staff use changes in basic measurements to give fluid according to a formal set of rules) and 'advanced haemodynamic monitoring' (where staff use equipment, such as specialized blood pressure monitoring devices placed into arteries, to guide how much fluid to give). These trials found no evidence that using one method instead of another reduces harm, including death or number of complications. One study suggests that length of stay in the hospital may be reduced if protocols or advanced haemodynamic methods are used, but because the number of people studied is not large, it is not possible to draw firm conclusions about this. No information was found regarding differences in the time taken for people to return to their previous type of accommodation or level of mobility. Two ongoing studies may provide more information in the future. The quality of evidence in a review may be high, moderate, low or very low. In this review, the evidence was assessed as being of low quality for all outcomes except time to medical fitness for discharge, for which the quality of evidence was moderate. Research findings to this point are insufficient to show how one can best optimize fluid levels in the large number of people around the world suffering from hip fracture. This is an update of a review published in 2004.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Advanced haemodynamic monitoring compared with protocol using standard measures for perioperative fluid volume optimisation

Patient or population: patients with proximal femoral fracture
Settings: emergency surgical care
Intervention: advanced haemodynamic monitoring
Comparison: protocol using standard measures such as CVP

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Protocol using standard measures such as CVP	Advanced haemodynamic monitoring				
All-cause mortality Follow-up: 30 days	**Moderate**[a]		**RR 0.52** (0.14 to 1.88)	61 (1 study)	⊕⊕◯◯ **low**[b,c]	
	66 per 1000	**34 per 1000** (9 to 124)				
Total length of hospital stay	The mean total length of hospital stay in the control groups was **13 days**	The mean total length of hospital stay in the intervention groups was **0.2 higher** (5.1 lower to 5.5 higher)		61 (1 study)	⊕⊕◯◯ **low**[b,c]	
Time to medical fitness for discharge	The mean time to medical fitness for discharge in the control groups was **10 days**	The mean time to medical fitness for discharge in the intervention groups was **2.3 lower** (5.9 lower to 1.3 higher)		61 (1 study)	⊕⊕◯◯ **low**[b,c]	
Adverse outcomes Cardiopulmonary- not reported	See comment	See comment	Not estimable	-	See comment	No data suitable for analysis available

Adverse outcomes - neurological Follow-up: 30 days	**Moderate**[d]		**RR 2.07** (0.2 to 21.61)	61 (1 study)	⊕⊕◯◯ **low**[b,c,e]
	10 per 1000	**21 per 1000** (2 to 216)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Based on mortality rate from Moppett 2012.
[b] Confidence intervals cross no effect and are consistent with increased as well as decreased risk.
[c] Estimate from one study only.
[d] Based on complication rates in Roche 2005 and Lawrence 2002.
[e] Estimate based on three events.

BACKGROUND

Description of the condition

Proximal femoral fractures (PFFs), or hip fractures, are fractures of the femur immediately distal to the articular surface of the hip joint, to about 5 cm below the lesser trochanter. They can be subdivided into intracapsular and extracapsular fractures. Intracapsular (also termed *transcervical* or *subcapital*) fractures occur proximal to the trochanteric line, and extracapsular (also termed *pertrochanteric*, *subtrochanteric*, *trochanteric* or *intertrochanteric*) fractures occur distal to the trochanteric line, up to 5 cm below the lower border of the lesser trochanter.

These fractures most commonly occur in elderly people with osteoporosis, following a simple mechanical fall. Approximately 1.5 million hip fractures are reported per year worldwide, with a projected increase to 4.5 million by 2050 (Gullberg 1997; Sterling 2011). Incidence varies by country, from about 50 to 500 per 100,000, and is about two times higher in females than males, although this difference varies with race (Kanis 2012; Kannus 1996). PFF is one of the most common orthopaedic emergencies, and most cases are managed by early surgical fixation to reduce complications from the prolonged immobility associated with conservative treatment. Limited evidence has been obtained from randomized controlled trials (RCTs) to inform this practice, but other types of studies have shown increased risk of death if surgery is delayed; it would be difficult to conduct ethically sound trials comparing operative with conservative treatment (Bottle 2006; Handoll 2008). Generally, medically fit patients should undergo surgery within 24 hours.

Undisplaced intracapsular fractures are usually treated by internal fixation to preserve the femoral head, with the use of screws or pins, with or without plates, to the femur. Displaced intracapsular fractures may be reduced and internally fixated or may undergo replacement arthroplasty. Extracapsular fractures may be fixed with a screw passed up the femoral neck to the head and then attached to a plate on the side of the femur, or an intramedullary nail may be used with a side screw passed up into the femoral head.

Description of the intervention

Age-related co-morbidities and dehydration in people presenting with PFF put them at increased risk for peritraumatic and perioperative complications. Providing adequate fluid resuscitation is important in minimizing this risk. The adequacy of fluid therapy may be determined by using simple, readily available clinical measures, such as tissue turgor, heart rate, blood pressure, urine output and central venous pressure (CVP). However, these are non-specific and poorly sensitive measures of fluid optimization (Marik 2008). Growing evidence suggests that predicting responsiveness to fluid therapy is more important (Funk 2009). The aim here is to use goal-directed fluid therapy to optimize cardiac output, to avoid overloading the cardiovascular system and precipitating heart failure. Alongside adequate haemoglobin and inspired oxygen levels, this optimizes delivery of oxygen to tissues and organs and may improve outcomes (Green 2010).

One way to assess fluid responsiveness is to use a protocol that combines several simple measures to determine the effect of a standardized fluid bolus and to decide whether additional fluid will provide benefit for the patient. Another method is to use advanced haemodynamic monitoring techniques to detect cardiovascular changes that occur with incremental fluid boluses, to predict responsiveness to increased fluid. Although some of these advanced techniques are in their infancy, a number have become established in clinical practice. These can be split into static measures of cardiac preload (the load placed on the heart by blood returning to it) and dynamic measures of interactions between heart and lung. Static measures aim to determine cardiac preload but fail to estimate the response to fluids in about one-half of patients, thus rendering them exposed to the hazards of unnecessary fluid therapy (Eyre 2010). Despite this, many of these measures are in clinical use. Right ventricular end-diastolic volume can be measured by fast-response thermistor pulmonary artery catheter or by cardiac scintigraphy. Transoesophageal echocardiography (TOE) can measure left ventricular (LV) end-diastolic area, which correlates well with left ventricular end-diastolic volume- a measure of LV preload. Transpulmonary thermodilution using a commercially available device (PiCCO, Pulsion Medical Systems) assesses global end-diastolic volume (GEDV), the largest volume of blood contained within the four heart chambers, and intrathoracic blood volume; both are validated as indicators of cardiac preload (Bendjelid 2010; Muller 2008). Pulmonary artery (Swan-Ganz) catheters are inserted into the pulmonary artery to measure pulmonary artery occlusion pressure (PAOP); however, their use has been reduced over recent years, as PAOP has been shown to be a poor marker of left ventricular end-diastolic volume, and therefore of cardiac preload and cardiac output (Maus 2008).

Dynamic measures are generally superior to static measures in predicting fluid responsiveness, although this has been demonstrated mainly in sedated ventilated patients (Eyre 2010). Various technologies use these measures, which include stroke volume variation (SVV), systolic pressure variation (SPV), pulse pressure variation (PPV), aortic blood velocity (ABV), superior vena cava collapsibility index (SVCCI) and inferior vena cava distensibility index (IVCDI). The commercially available LiDCO device (Vigileo) analyses the waveform of the arterial blood pressure pulse for SVV, SPV and PPV; transthoracic echocardiography (TTE) measures IVCDI; oesophageal Doppler measures SVV and ABV; TOE can measure SVCCI and ABV; and PiCCO can measure SVV. LiDCO and TTE can be used with patients who are awake when undergoing regional anaesthesia and with those who are unconscious when undergoing general anaesthesia. Oesophageal Doppler and TOE can be used only with patients who are undergoing general

anaesthesia.

How the intervention might work

Major surgery and critical illness are associated with increased oxygen demand due to a systemic inflammatory response, the stress response, and increased metabolic activity. Inadequate fluid resuscitation and cardiopulmonary disease may reduce the supply of adequate tissue blood flow and delivery of oxygen. This may result in cellular dysfunction, organ damage, organ failure and ultimately death. Fluid overload is also harmful, potentially causing cardiac performance to fall as the result of extreme right shift on the Starling myocardial performance curve, respiratory failure due to fluid accumulation in the lungs, gastric dysmotility and poor wound healing. Growing evidence indicates that standardized methods to optimize fluid and oxygen delivery to tissues may decrease morbidity and mortality in a variety of clinical settings, particularly among high-risk surgical patients and those with critical illness or sepsis (Lees 2009).

Why it is important to do this review

Protocols, or advanced methods for managing fluid therapy, may improve various outcomes in the large number of people who suffer from PFF each year. However, these methods also have the potential for harm and incur financial cost. A systematic evaluation of the current evidence is needed to assist clinicians in attempting to optimize fluid volume status in people undergoing surgery for PFF. The outcomes that we included were selected according to their frequency of use in studies of PFF and their usefulness in clinical decision making (Liem 2012).

This is an update to a Cochrane review first published in 2004 (Price 2004). Because new monitoring techniques and revised methods have been introduced within The Cochrane Collaboration, we have re-run the searches, including extra search terms, and have used different methods to assess study quality.

OBJECTIVES

To compare the safety and effectiveness of different methods of perioperative fluid optimization in adult participants undergoing surgical repair of hip fracture. We considered the following methods: advanced invasive haemodynamic monitoring, such as transoesophageal Doppler and pulse contour analysis; a protocol using standard measures, such as blood pressure, urine output and central venous pressure; and usual care.

Comparisons of fluid types (e.g. crystalloid vs colloid) and other methods of optimizing oxygen delivery, such as blood product therapies and pharmacological treatment with inotropes and vasoactive drugs, are considered elsewhere.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials (RCTs), including cluster-randomized trials. Quasi-randomized trials (e.g. alternation) and trials in which treatment allocation was inadequately concealed were also considered for inclusion. We included unpublished studies and studies published only in abstract form if adequate method and results data could be obtained. We did not expect to identify any cross-over trials for this condition.

Types of participants

We included studies on adults who underwent acute surgical treatment of any type for PFF while under regional or general anaesthesia.

Types of interventions

We included studies that compared the use of any two of the following.

- Advanced invasive haemodynamic monitoring, such as transoesophageal Doppler and pulse contour analysis.
- A protocol using standard measures, such as blood pressure, urine output and central venous pressure.
- Usual care.

We undertook reviews of three different comparisons.

- Advanced haemodynamic monitoring versus a protocol using standard measures.
- Advanced haemodynamic monitoring versus usual care.
- A protocol using standard measures versus usual care.

Types of outcome measures

Primary outcomes

- All-cause mortality (within 30 days if reported, otherwise as reported in the trial).
- Length of hospital stay.
    - Total length of hospital stay.
    - Time to medical fitness for discharge.
- Return of participant to pre-fracture category of accommodation at six months.
- Return to pre-fracture mobility at six months.

Secondary outcomes

- Major adverse events in hospital.

    - Iatrogenic (related to intervention, e.g. pneumothorax, haemothorax, upper limb thrombosis, line sepsis, local haematoma).
    - Cardiopulmonary (e.g. myocardial infarction, cardiac or respiratory failure, thromboembolic event).
    - Neurological (e.g. delirium, postoperative cognitive dysfunction, cerebrovascular accident).

We also recorded any complications reported in the study, including minor events.
Outcomes did not form part of the study eligibility assessment. Studies that met design, participant and intervention criteria were included in the review even if they did not report any relevant outcomes.

Search methods for identification of studies

Electronic searches

We searched for relevant randomized trials published in any language. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2012, Issue 10, see Appendix 1); MEDLINE via Ovid SP (1966 to October 2012, see Appendix 2); and EMBASE via Ovid SP (1982 to October 2012, see Appendix 3). For searching in MEDLINE, we combined our topic-specific key words with the Cochrane highly sensitive search strategy for identifying RCTs (Higgins 2011). We modified this filter for use in EMBASE and used specific keywords to identify potential studies (see Appendix 1; Appendix 2; Appendix 3).
We searched for ongoing clinical trials and unpublished studies on the following Internet sites (on 19 October 2012).

- ClinicalTrials.gov trials registry (see Appendix 4).
- The World Health Organization's International Clinical Trials Registry Platform (see Appendix 5).

Searching other resources

We undertook backward and forward citation searching for key review articles identified through the initial searches (see Appendix 6). We used Web of Science for forward citation searching. We read the reference lists of articles selected for backward citation, paying particular attention to the articles included in systematic reviews.
We contacted investigators to ask for details of ongoing studies and any unpublished data needed for our analyses.

Data collection and analysis

Selection of studies

Two review authors (AB, AN) independently screened all titles and abstracts identified by the searches (to October 2012) for potentially eligible trials. A pilot screening of 100 articles was performed initially to clarify criteria for discarding articles at this stage. We removed studies that were very unlikely to be eligible. If no abstract was available but the title was possibly relevant, the full text of the article was obtained. Then the full texts of all remaining articles were independently examined by the same review authors. A joint decision was made at that time regarding inclusion, with disagreements resolved by a third review author (AFS).

Data extraction and management

AB (content area specialist) and AN (methodologist) independently extracted and collected data on a standardized paper form (see Appendix 7). No blinding of the author, the institution or the publication source of the studies was performed. If relevant information or data were not available in the paper, we contacted the lead author to request additional details. We resolved disagreements by discussion and consensus, and finally with the involvement of a third review author (AFS).
Multiple reports of the same study were extracted directly onto a single data collection form, thereby constructing a composite data set for that study.

Assessment of risk of bias in included studies

Two review authors (AB, AN) independently assessed risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011a). The following six domains were assessed: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting.
Blinding and incomplete outcome data were considered separately for each outcome. Blinding of participants was of particular importance for patient-reported outcomes such as mobility. Blinding of assessors was particularly important for outcomes such as cognitive function that may be prone to detection bias.

Measures of treatment effect

For dichotomous outcomes (e.g. mortality, adverse outcomes), we entered numbers of events and total number within each randomization group into RevMan 5.1 (RevMan 5.1) and calculated risk ratios (RRs) with 95% confidence intervals (CIs) to express the effect size. If data were presented in other forms, such as hazard or odds ratios, and if we were unable to obtain the required tabular data from the study authors, we planned to enter these and to use the generic inverse variance option in RevMan 5.1. For continuous

measures, such as length of stay, weighted mean differences were calculated if means and standard deviations were available. Standard deviations were calculated from 95% CIs using the methods described in Section 7.7.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Unit of analysis issues

For any cluster trials included, we extracted data directly only if the analysis properly accounted for the cluster design, using methods such as multi-level modelling or generalized estimating equations. If these adjustments were not made within the report, we performed approximate analyses by recalculating standard errors or sample sizes based on the design effect (Section 16.3.6, Higgins 2011). The resulting effect estimates and their standard errors were analysed using the generic inverse variance method in RevMan 5.1 (RevMan 5.1).

In studies in which participants were randomly assigned to multiple intervention groups, each pair-wise comparison was made separately but with shared intervention groups divided out approximately among the comparisons. For example, if multiple intervention groups shared a common control group, the number of participants and the number of events in the control group were divided equally; thus the number of subgroups in the control group matched the number of intervention groups (Higgins 2011).

Dealing with missing data

We attempted to contact the first author or the contact person for all trials with missing data before making a decision about trial eligibility. A modified intention-to-treat (ITT) analysis was undertaken, and all participants who did not withdraw consent for trial inclusion before the time of surgery were included. For missing outcome data, where possible, we compared the effects of complete case analysis, worst case scenario and last observation carried forward options on the results of any individual study and on any meta-analysis undertaken.

Assessment of heterogeneity

The trials that were found may not have been carried out according to common protocols, thus introducing differences in participant groups, clinical settings, concomitant care, etc. Important potential sources of heterogeneity include participant characteristics, differences in control or intervention protocols and duration of perioperative fluid optimization.

Heterogeneity between studies was described on the basis of participant group, setting and type of intervention. This was then assessed statistically when data allowed, using the Chi^2 test and the I^2 statistic. Important heterogeneity (Chi^2 $P < 0.1$ and $I^2 > 50\%$) was investigated, when possible, by subgroup analyses and by meta-regression.

Assessment of reporting biases

Reporting bias may occur within studies, with certain outcomes not reported. When a report or the original protocol suggested that data on an outcome were collected but were not reported in the paper, we contacted the authors to request the data.

When an adequate number of trials had been identified for inclusion, funnel plots were constructed and were examined visually to assess the presence of publication bias; Egger's test was used to test for asymmetry.

Data synthesis

We attempted meta-analysis for outcomes for which we had comparable effect measures from more than one study and when measures of heterogeneity indicated that pooling of results was appropriate. A value of $I^2 > 80\%$ would argue against presentation of an overall estimate. When we had identified sufficient studies to allow combination of results, differences between studies related to duration and methods of fluid optimization and participant characteristics were likely to suggest that random-effects models would be the most suitable choice. Mantel-Haenszel models were used when possible for dichotomous outcomes.

Subgroup analysis and investigation of heterogeneity

If data were sufficient, we investigated the following subgroups, which may account for heterogeneity between studies.

- Duration of monitoring and protocol use.
- Timing of outcome measurement. If the timing of outcome measures varied between studies, then the outcome was analysed only as a subgroup analysis.

Any differences in effect size between subgroups were assessed in RevMan, using I^2 estimates (Higgins 2011).

Sensitivity analysis

When possible, we performed the following sensitivity analyses.

- Reanalysis excluding studies with a high risk of bias.
- Reanalysis excluding unpublished studies.

Summary of findings table

We used the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with the specific outcomes in our review.

- All-cause mortality.
- Length of hospital stay.
- Return to pre-fracture category of accommodation at six months.
- Return to pre-fracture mobility at six months.
- Major adverse events in hospital.

We constructed a 'Summary of findings' (SoF) table by using the GRADE software (gradepro.org). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence is based on within-study risk of bias (methodological quality), the directness of the evidence, the heterogeneity of the data, the precision of effect estimates and the risk of publication bias.

RESULTS

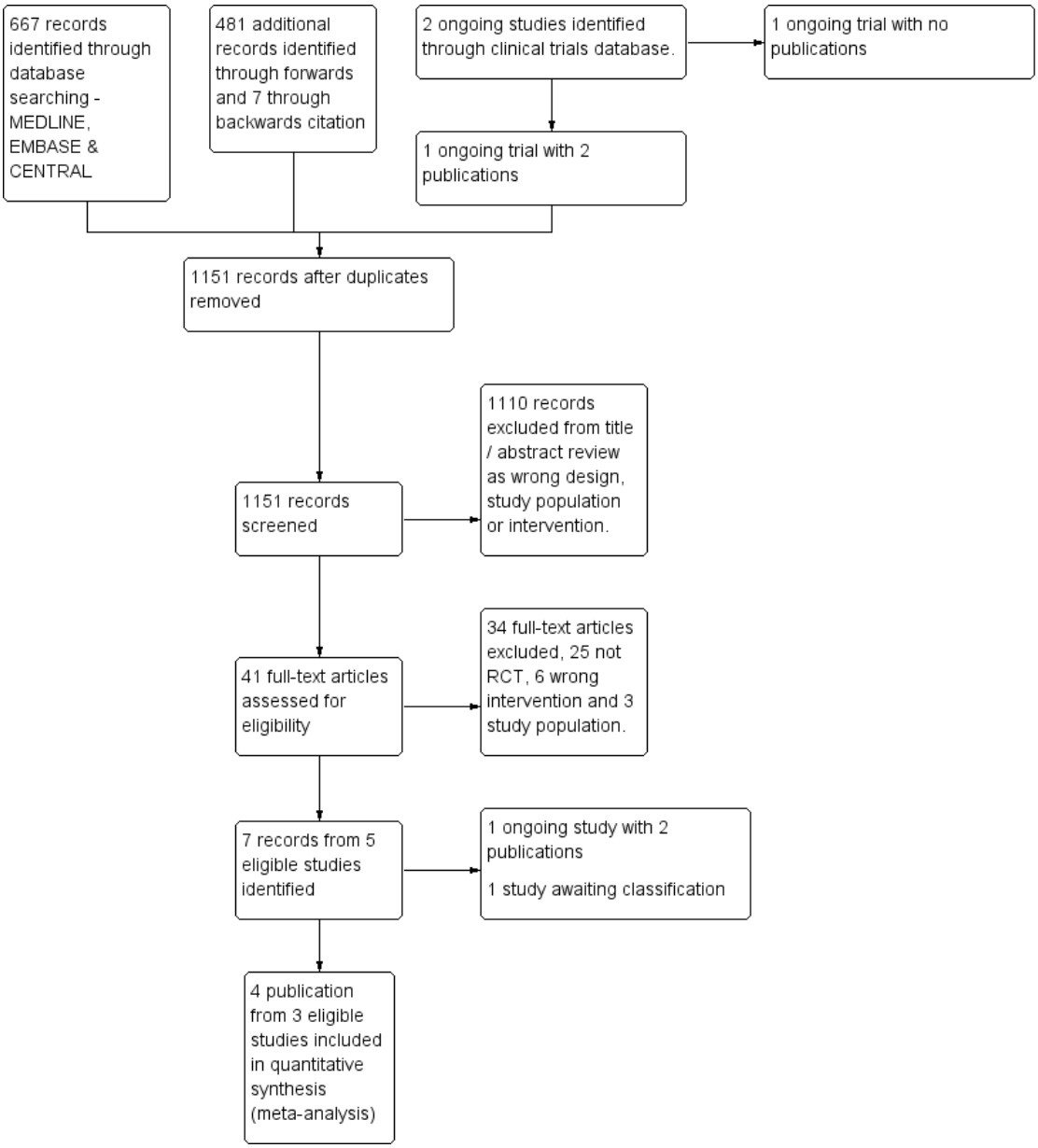
Description of studies

Results of the search

See Characteristics of included studies; Characteristics of ongoing studies; Characteristics of studies awaiting classification.

Searches of electronic databases revealed 667 records. An additional seven records were identified from the references of potentially relevant articles (backwards citation), and 481 had cited important articles (forward citation). Searches of clinical trials databases identified two ongoing studies, one of which had two publications. A total of 1151 unique titles and/or abstracts were reviewed, and 41 publications met the criteria for further assessment. From these, we included three trials that randomly assigned a total of 200 participants (Schultz 1985; Sinclair 1997; Venn 2002). One study is awaiting classification (see Figure 1).

Figure 1. I Study flow diagram.



Included studies

None of the three included trials were published in abstract form only (see Characteristics of included studies). All trials included solely adult participants who were undergoing surgery for PFF. Two trials were conducted in the UK (Sinclair 1997; Venn 2002) and one in the USA (Schultz 1985). All were published in the English language. The interval between the first and the last trial was approximately 17 years. Ages of participants ranged from 40 to 102 years. Each trial made different comparisons: Swan-Ganz monitoring versus CVP monitoring (Schultz 1985); oesophageal Doppler monitoring versus conventional fluid management (Sinclair 1997); and oesophageal Doppler monitoring versus CVP monitoring versus conventional fluid management (Venn 2002). These trial comparisons correspond to the following comparisons in our review: advanced haemodynamic monitoring (Swan-Ganz, oesophageal Doppler); a protocol using standard measures (CVP monitoring); and usual care (conventional fluid management). Two trials studied only intraoperative fluid optimization (Sinclair 1997; Venn 2002); one trial studied preoperative, intraoperative and postoperative fluid optimization (Schultz 1985). All participants underwent general anaesthesia, although this was not explicitly stated in one trial (Schultz 1985). The surgical techniques used to treat PFF included dynamic hip screw, arthroplasty and AO cannulated screw. All trials investigated mortality, although at different time points: undefined "postoperative" (Schultz 1985) and in-hospital (Sinclair 1997; Venn 2002). We excluded in-hospital deaths that occurred more than 30 days postoperatively (Sinclair 1997). On the basis of total hospital stays and ranges reported in Venn 2002, we assumed that all deaths and adverse events in this trial occurred within 30 days of operation. Two trials compared both total length of hospital stay and time until medically fit for discharge (Sinclair 1997; Venn 2002). One reported as medians and interquartile ranges (Sinclair 1997), and the other as means with 95% confidence intervals (Venn 2002). We calculated standard deviations using the formula for the T distribution in Section 7.7.3.2 in Higgins 2011. Two trials investigated morbidity, although the time frame for Schultz was described only as postoperative (Schultz 1985; Venn 2002). In Venn 2002, postoperative adverse events were reported, but data were given as episodes of cardiopulmonary events rather than as numbers of participants, so we were not able to calculate risk ratios. Two trials compared changes in intraoperative physiological parameters (Sinclair 1997; Venn 2002). One trial compared both time from admission to surgery and length of operation (Schultz 1985).

Ongoing studies

Two studies are ongoing. The first is comparing routine perioperative fluid therapy and goal-directed haemodynamic therapy in terms of morbidity, mortality, length of hospital stay, activity of daily living, health-related quality of life, cognitive function and the need for social services until 12 months postoperatively after fixation of PFF in elderly participants (GDHT study). The second is comparing stroke volume- guided intraoperative fluid management using a calibrated cardiac output monitor (LiDCOplus) against routine fluid administration in terms of length of acute hospital stay, numbers of complications and total costs of care (NOTTS study; Characteristics of ongoing studies).

Studies awaiting classification

One study that included a mixed high-risk surgical population is awaiting classification; we have been unable to contact the authors to request adequate data about participants within the orthopaedic group who were treated for PFF (Sandham 2003; Characteristics of studies awaiting classification).

Excluded studies

We excluded 34 full text articles identified for further assessment (Figure 1). These articles provided the wrong intervention, included the wrong study population or were not RCTs. Specific groups of excluded trials were those investigating blood product transfusion strategies, vasopressor therapies and bundles of perioperative care, including nursing care, rehabilitation and nutritional strategies. Eight RCTs that were excluded because of incorrect intervention or participant group are described in the Characteristics of excluded studies table.

Risk of bias in included studies

The various bias domains are presented in the 'Risk of bias' graph and a 'Risk of bias' summary figure. The risk of bias was evaluated on the basis of major sources of bias (domains), as described above. For a more detailed description of individual trial qualities, see Characteristics of included studies (see Figure 2, Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

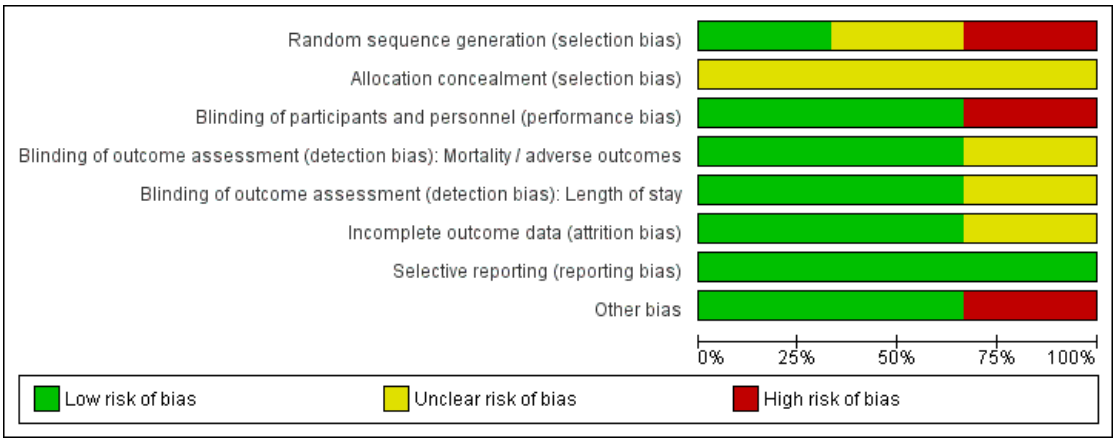
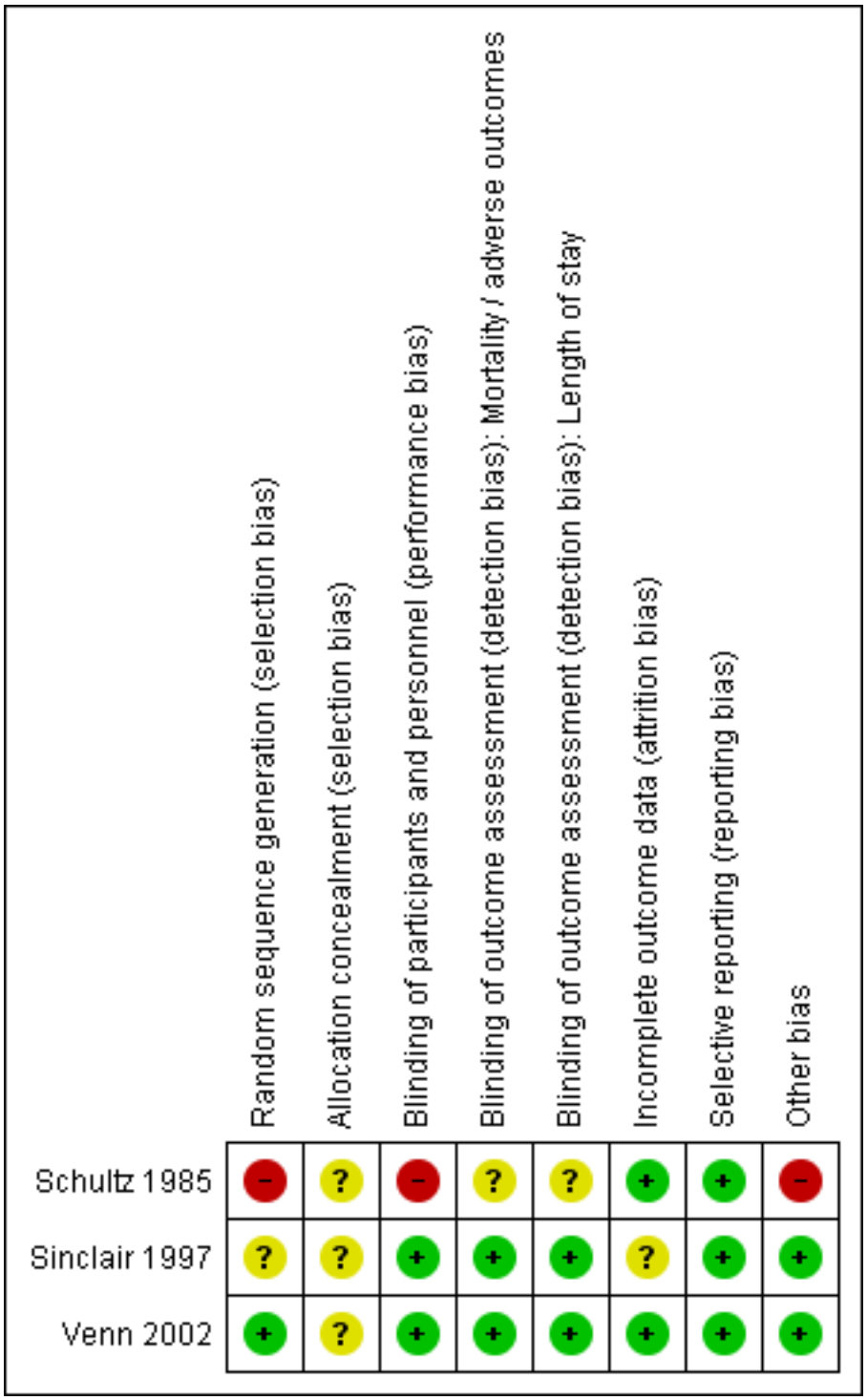


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The methods used for random sequence generation were adequately reported in only one study (Venn 2002) and were inadequately reported or questionable in two studies (Schultz 1985; Sinclair 1997). Allocation concealment was not adequately reported in any study.

Blinding

Defining adequate blinding in trials of fluid optimization was challenging. Two trials were pragmatic in their attempts to blind the primary anaesthetist in theatre to fluid administered (performance bias), as it would not be practical in our view to safely blind the attending clinician to this (Sinclair 1997; Venn 2002); no information was provided about blinding of the operating surgeon(s) in any trial. Two trials provided enough information to allow assessment of blinding of outcome assessment (detection bias) as adequate (Sinclair 1997; Venn 2002). One trial provided no information about blinding of participants, attending clinicians or investigators (Schultz 1985) (see Characteristics of included studies).

Incomplete outcome data

Complete follow-up was reported for mortality, morbidity, adverse events and length of stay for two trials (Sinclair 1997; Venn 2002). One trial provided no information about exclusions due to deviations from protocol (Schultz 1985). No participant was lost to follow-up. Only one trial explicitly performed analyses in accordance with the ITT method (Venn 2002) (see Characteristics of included studies).

Selective reporting

Two trials reported all expected outcomes (Sinclair 1997; Venn 2002). One trial provided inadequate information about expected outcomes; therefore we assessed the risk of selective reporting as unclear (Schultz 1985) (see Characteristics of included studies).

Some of our analyses were subject to limitations because length of stay data were published in graphical form without adequate corresponding numerical data (Sinclair 1997). One trial did not provide details on length of follow-up in terms of mortality, but data were sufficient for analysis; data regarding morbidity and adverse events were adequate (Schultz 1985).

Other potential sources of bias

One trial received support from the Special Trustees of the Middlesex Hospital, defined as not-for-profit (Sinclair 1997). Funding sources for the remaining trials were defined as unknown. Sample size calculation was reported in two trials (Sinclair 1997; Venn 2002). No trial was stopped early as the result of benefits or difficulty in recruiting participants. Trials were too few to permit construction of funnel plots to facilitate assessment of publication bias, or to perform Egger's test for asymmetry.

Analyses of the benefits of fluid optimization in this group of participants were limited by differences in study design. Two trials involved intraoperative optimization (Sinclair 1997; Venn 2002). One involved both intraoperative and postoperative optimization and was seriously limited by the fact that no detail was given about the protocol used (Schultz 1985). Between trials, differences were noted in outcome definitions, in time points for mortality and length of stay reporting and in types of adverse events reported. In addition, all trials involved relatively low numbers of participants (see Characteristics of included studies).

Effects of interventions

See: **Summary of findings for the main comparison** Advanced haemodynamic monitoring compared with protocol using standard measures for perioperative fluid volume optimisation; **Summary of findings 2** Advanced haemodynamic monitoring compared with usual care for perioperative fluid optimization; **Summary of findings 3** Protocol using standard measures such as CVP compared with usual care for perioperative fluid optimization See also Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3.

Comparison 1. Advanced haemodynamic monitoring vs protocol using standard measures

All-cause mortality

Two trials reported mortality (Schultz 1985; Venn 2002). For one study, the follow-up period was unclear but was reported as "postoperative" (Schultz 1985), so we were unable to pool results. This trial showed a significant reduction in mortality (RR 0.1, 95% CI 0.01 to 0.74; 70 participants, one trial); however, we had serious concerns about its quality (Schultz 1985). In the other study (Venn 2002), the time frame for death was described as postoperative, and the results were consistent with both increased and decreased risk of mortality in the intervention group (RR 0.52, 95% CI 0.14 to 1.88; 61 participants, one trial). (See Analysis 1.1.)

Length of hospital stay

Only one trial reported this outcome, and it found that the mean difference for hospital stay was 0.2 days longer in the advanced haemodynamic group (95% CI 5.1 days shorter to 5.5 days longer; 61 participants, one trial) and for time to medical fitness was 2.30

days shorter (95% CI 5.90 days shorter to 1.30 days longer; 61 participants, one trial) (Venn 2002; Table 1).

Return of participant to pre-fracture category of accommodation at six months; return to pre-fracture mobility at six months

No trial reported data for these outcomes.

Major adverse events in hospital

Two trials investigated complications, reporting overall morbidity and cardiovascular or neurological outcomes; however, iatrogenic events were not reported by intervention/control groups (Schultz 1985; Venn 2002). Once again, it was not possible to pool data because of the unclear period of follow-up in Schultz 1985. Both studies reported results consistent with increased and decreased risks of adverse events in the intervention groups. In Venn 2002, the relative risk for neurological events was 2.07 (95% CI 0.20 to 21.61) and for all complications 0.90 (95% CI 0.37 to 2.18) (Table 2). (See Analysis 1.2.)

Comparison 2. Advanced haemodynamic monitoring vs usual care

All-cause mortality

Two trials reported in-hospital mortality (Sinclair 1997; Venn 2002). We excluded two deaths from Sinclair 1997, one each from the intervention and control groups, as they occurred more than 30 days postoperatively. Only three deaths were reported in each group, and the pooled results are consistent with both increased and decreased risks of mortality in participants who received advanced haemodynamic monitoring (RR 1.03, 95% CI 0.23 to 4.66; 99 participants, two trials). (See Analysis 2.1.)

Length of hospital stay

Two trials investigated both total hospital stay and time to medical fitness for discharge (Sinclair 1997; Venn 2002). One trial found a reduction in time to medical fitness for discharge (6.20 days shorter, 95% CI 10.1 to 2.30 days shorter; 59 participants, one trial), but not for total inpatient stay (4.00 days shorter, 95% CI 9.93 days shorter to 1.93 days longer; 59 participants, one trial), in the advanced haemodynamic group (Venn 2002; Table 2). The other trial provided data in the form of median and interquartile ranges, which were not suitable for inclusion in a meta-analysis (Sinclair 1997; Table 3), but reported a reduction of five days in median time to fitness for discharge (from 15 to 10 days) and a reduction of eight days in total hospital stay (from 20 to 12); the authors reported significant differences at $P < 0.05$ (Mann Whitney U test). Hence no meta-analysis was carried out, and only a narrative summary is offered for this outcome.

Return of participant to pre-fracture category of accommodation at six months; return to pre-fracture mobility at six months

No trial reported data for these outcomes.

Major adverse events in hospital

These were reported by only one trial, and results were consistent with increased and decreased risk in participants who had received advanced haemodynamics monitoring for neurological events (RR 1.93, 95% CI 0.19 to 20.18; 59 participants, one trial) and for all complications (RR 0.48, 95% CI 0.23 to 1.02; 59 participants, one trial) (Venn 2002; Table 2).

Comparison 3. A protocol using standard measures vs usual care

All-cause mortality

Only one trial reported on this outcome (Venn 2002) and found no difference in mortality between participants who received care according to the protocol and standard care (RR 2.81, 95% CI 0.61 to 12.81; 60 participants, one trial) (Table 4).

Length of hospital stay

One trial reported a reduction in time to medical fitness (3.9 days shorter, 95% CI 7.05 to 0.75 days shorter; 60 participants, one trial) but not in total hospital stay (4.2 days shorter, 95% CI 11.0 days shorter to 2.60 days longer; 60 participants, one trial) (Venn 2002; Table 4).

Return of participant to pre-fracture category of accommodation at six months; return to pre-fracture mobility at six months

No trial reported data for these outcomes.

Major adverse events in hospital

These were reported by only one trial, and results were consistent with increased and decreased risk in participants who had received care according to a protocol for neurological events (RR 0.94, 95% CI 0.06 to 14.27; 60 participants, one trial) and for all complications (RR 0.53, 95% CI 0.26 to 1.08; 60 participants, one trial) (Venn 2002; Table 4).

Subgroup and sensitivity analyses

We were particularly concerned about the quality of one study in terms of the risk of bias (Schultz 1985). No details were given about methods of randomization, and important baseline differences between intervention and control groups were noted. In addition, the nature of intervention was not fully reported, and staff were not blinded to the intervention group (see Characteristics of included studies). Because only two studies were included in the comparison of advanced haemodynamic monitoring, we were not able to perform sensitivity analyses; however, we have included results from Venn 2002 in the 'Summary of findings' tables.

We obtained no unpublished data, and so it was not possible to carry out this subgroup analysis.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Advanced haemodynamic monitoring compared with usual care for perioperative fluid optimization

Patient or population: patients with proximal femoral fracture
Settings: emergency surgical care
Intervention: advanced haemodynamic monitoring
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Advanced haemodynamic monitoring				
All-cause mortality Follow-up: 30 days	**Moderate**[a]		**RR 1.03** (0.23 to 4.66)	99 (2 studies)	⊕⊕◯◯ **low**[b,c]	
	66 per 1000	**68 per 1000** (15 to 308)				
Total length of hospital stay	The mean total length of hospital stay in the control groups was **18 days**	The mean total length of hospital stay in the intervention groups was **4 lower** (9.93 lower to 1.93 higher)		59 (1 study)	⊕⊕◯◯ **low**[b,c]	
Time to medical fitness for discharge	The mean time to medical fitness for discharge in the control groups was **14 days**	The mean time to medical fitness for discharge in the intervention groups was **6.2 lower** (10.1 to 2.3 lower)		59 (1 study)	⊕⊕⊕◯ **moderate**[c]	

Adverse outcomes Cardiopulmonary - not reported	See comment	See comment	Not estimable	-	See comment	No data suitable for analysis available
Adverse outcomes - neurological Follow-up: 30 days	**Moderate**[d] **10 per 1000**	**19 per 1000** (2 to 202)	**RR 1.93** (0.19 to 20.18)	59 (1 study)	⊕⊕◯◯ **low**[b,c]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Based on mortality rate from Moppett 2012.
[b] Confidence interval crosses no effect and does not rule out an increased risk.
[c] Estimate based on small number of events and/or single study.
[d] Based on complication rates in Roche 2005 and Lawrence 2002.

Protocol using standard measures such as CVP compared with usual care for perioperative fluid optimization

Patient or population: patients with proximal femoral fracture
Settings: emergency surgical care
Intervention: protocol using standard measures such as CVP
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Protocol using standard measures such as CVP				
All-cause mortality Follow-up: 30 days	**Moderate**[a]		**RR 2.81** (0.61 to 12.81)	60 (1 study)	⊕⊕◯◯ **low**[b]	
	66 per 1000	**185 per 1000** (40 to 845)				
Total length of hospital stay	The mean total length of hospital stay in the control groups was **18 days**	The mean total length of hospital stay in the intervention groups was **4.2 lower** (11 lower to 2.6 higher)		57 (1 study)	⊕⊕◯◯ **low**[b]	
Time to medical fitness for discharge	The mean time to medical fitness for discharge in the control groups was **14 days**	The mean time to medical fitness for discharge in the intervention groups was **3.9 lower** (7.05 to 0.75 lower)		57 (1 study)	⊕⊕⊕◯ **moderate**[c]	
Adverse outcomes Cardiopulmonary- not reported	See comment	See comment	Not estimable	-	See comment	Data suitable for analysis not available

Adverse outcomes - neurological	**Moderate**[d]		**RR 0.94** (0.06 to 14.27)	60 (1 study)	⊕⊕◯◯ **low**[b]
	10 per 1000	**9 per 1000** (1 to 143)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Based on mortality rate from Moppett 2012.
[b]Based on one study with small number of events. Confidence intervals cross no effect and are consistent with increased as well as decreased risk.
[c]Based on one study with small number of participants.
[d]Based on complication rates in Roche 2005 and Lawrence 2002.

DISCUSSION

Summary of main results

The conclusions of this updated review remain the same as those of the original review (Price 2004). We did not find a benefit for the use of fluid optimization strategies in participants undergoing surgery for PFF in terms of mortality or adverse events. We did find a possible benefit in terms of length of hospital stay; however, only limited data are available. Furthermore, we were unable to conduct relevant subgroup and sensitivity analyses because of lack of data. Currently, no convincing evidence of safety or effectiveness is available to support the routine use of advanced monitoring or protocols to guide fluid therapy in adult patients undergoing surgery for PFF. Length of hospital stay may be reduced, but the evidence is not strong enough to allow evidence-based recommendations to be made regarding fluid optimization in this patient group (see also Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

Overall completeness and applicability of evidence

Since the time of the original review, the method of reporting Cochrane systematic reviews has changed; therefore we re-ran our search strategy from the inception of the databases, rather than using the date of the previous search. Despite this, we found no new published studies to include, and it is clear that good quality clinically relevant evidence on this subject is insufficient. We did identify at least two ongoing studies, and it is hoped that they will provide more data in the near future (see Characteristics of ongoing studies).

Among the three studies and 200 participants analysed, outcome data were variable in terms of quality and definition. Each trial reported mortality data, but they were defined by different time points or were not defined at all. Only one study reported an *a priori* power calculation for mortality (Sinclair 1997). It is arguable that any mortality reduction due to the interventions in our review would be small because of the many other factors that put PFF patients at relatively high risk of death. If an in-hospital mortality of 6.6% is assumed (Moppett 2012), a study with 80% power to detect a 50% decrease in in-hospital mortality (from 6.6% to 3.3%) would require randomization of 678 participants into each group (α = 0.05). Therefore much larger studies than the ones presented in this review are likely to be needed to show benefit derived from these interventions. Similarly, to detect a 50% reduction in adverse event incidence (from 15% to 7.5%) (Lawrence 2002; Roche 2005), 278 participants would be required for each group. On the other hand, the two studies investigating length of stay were adequately powered (Sinclair 1997; Venn 2002).

Other outcomes were investigated only by one or two trials, or not at all, making it difficult for investigators to draw conclusions. It could be contested that we should have looked at outcomes of greater "orthopaedic relevance", but these tend to be reported over the longer term, and it seems logical to assume that intraoperative fluid optimization is more likely to affect shorter-term in-hospital outcomes. Whilst these may influence longer-term outcomes, it would be more difficult for studies to gain evidence of such effects over longer time periods in the presence of other confounding factors. This may be why studies have not investigated time to return to pre-fracture mobility/accommodation.

Caution should be exercised in the applicability of our results in countries that are less well developed. Furthermore, it should be appreciated that usual care in some countries, or even between clinicians in the same hospital, may differ.

Quality of the evidence

Our review has several limitations, and our findings are limited by the quality and quantity of available evidence. All trials recruited participants from similar populations in well-developed countries, but detail was not uniformly provided about the interventions that we investigated, particularly the protocol used in the trial by Schultz et al (Schultz 1985). As has been mentioned, the quality of outcome reporting was variable. Mortality data were reported but to different time points, making combination of data from different studies impossible for a single comparison (Analysis 1.1). The two trials reporting significant differences in time to medical fitness for discharge include relatively low numbers (130 participants) (Sinclair 1997; Venn 2002), and in one trial, length of stay data were estimated from graphical data, which we were unable to incorporate into a meta-analysis (Sinclair 1997). No trials reported on two of our primary outcome measures: time to return to pre-fracture mobility and accomodation. The secondary outcome of adverse events was reported only well enough to allow analysis for the neurological event subgroup and total adverse events, and again was limited to only one or two trials, depending on the comparison. The data were not reported well enough to allow analysis of subgroups of iatrogenic and cardiopulmonary events. We were unable to contact the authors of included trials to ask for unpublished outcome data. Trials were too few to permit subgroup, heterogeneity or sensitivity analyses to be performed.

Lack of available information therefore significantly limits this systematic review. Broadening the scope of the review to include a greater number of clinical groups would increase the data set but would be clinically less useful to the reader interested in the specific management of PFF. It would also further increase heterogeneity. It is hoped that this can be avoided in the future when ongoing and future studies are published (see Characteristics of ongoing studies), or when additional data from existing studies become available (see Characteristics of studies awaiting classification).

Potential biases in the review process

To the best of our knowledge, no potential biases arose from the review process.

Agreements and disagreements with other studies or reviews

The authors of the original version of this review stated that invasive methods of fluid optimization may shorten hospital stay, but their effects on other important, patient-centred, longer-term outcomes are uncertain. We would agree in general with this but urge caution in the interpretation of hospital stay data that are limited in scale and in some cases are not adequate for detailed analysis. We are not aware of any other good quality studies or systematic reviews investigating perioperative fluid optimization after PFF.

AUTHORS' CONCLUSIONS

Implications for practice

Weak evidence of low quality is available to support or reject the hypothesis that fluid volume optimization improves mortality or complication rates for patients with PFF, whether advanced haemodynamic monitoring or protocols based on standard measures are used. Some evidence suggests that time to medical fitness for discharge may be improved, but data are sparse and of only moderate quality.

Implications for research

It is disappointing that no new high-quality studies have been performed in the eight years since this review was last prepared; we hope that ongoing studies will provide further information for future updates of this review (Characteristics of ongoing studies). Enough evidence of potential benefit has been derived from studies of fluid optimization in other patient groups (Lees 2009) to justify additional large RCTs with low risk of bias in participants with PFF. These should be powered adequately to allow detection of differences in the outcome measures that are most important to patients and clinicians, including short-term mortality, morbidity and length of stay; longer-term mortality; and patient-centred quality of life outcomes, such as return to pre-fracture mobility and accommodation. With additional data, subgroup analysis may reveal differences between interventions that optimize fluid status before, during or after surgery.

Finally, it would be useful to assess the use of fluid optimization strategies within enhanced recovery programmes for PFF. These programmes comprise multifactorial bundles of care that are becoming more widely used across a range of clinical conditions, although the level of evidence of benefit is still low (Hoffman 2012). This assessment would have the benefit of controlling many of the confounding factors that limit studies comparing advanced monitoring or protocols against usual care.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Schultz 1985

Methods	Publication type: full article Allocation random: unclear Allocation concealment: unclear Baseline comparison: yes Baseline similarity: monitored group older than non-monitored; differences in time to surgery Blinding of care givers: unclear Additional features to blind fluid administered: unclear Control of co-interventions: unclear Completeness of follow-up: unclear Intention-to-treat analysis: unclear
Participants	Location: Westchester County Medical Centre, NY, USA Centre: single centre Language: English Inclusion criteria: intracapsular and extracapsular hip fractures; specifics not described Exclusion criteria: not described Age: monitored group mean 78 (range 40 to 95), non-monitored group mean 67 (range 40 to 89) Number randomly assigned: 70 Number that completed the study: 70 ASA grade: not described Surgery type: Extracapsular fractures underwent open reduction and internal fixation using a sliding compression screw and side plate; intracapsular fractures were treated by hemiarthroplasty
Interventions	Monitored group: implied that GA was given. Swan-Ganz catheter was inserted, and systolic pressures in RA, RV and PA and PA wedge pressures were measured. Cardiac output was optimized with fluids, exact methods were unclear. Repeated until 1 to 2 days after surgery Non-monitored group: implied that GA was given. CVP was inserted, fluids as per protocol, exact management unclear
Outcomes	Morbidity Mortality- time point not defined Time from admission to surgery Mean length of operation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Schultz 1985 (*Continued*)

Random sequence generation (selection bias)	High risk	Paper states that participants were assigned on a random basis on admission to hospital. No details given. Large differences in groups at baseline
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information about whether clinical staff in operating theatre or on ward were aware of participant allocation. This seems unlikely. Intervention not clearly defined
Blinding of outcome assessment (detection bias) Mortality / adverse outcomes	Unclear risk	No information about how outcomes were assessed and no definitions
Blinding of outcome assessment (detection bias) Length of stay	Unclear risk	Outcome not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomly assigned participants included in analyses. No information about exclusions due to deviations protocol
Selective reporting (reporting bias)	Low risk	Outcomes not fully described
Other bias	High risk	Serious baseline imbalances between monitored and non-monitored group raise questions about the randomization procedure; methods not fully clear; outcomes not fully defined

Sinclair 1997

Methods	Publication type: full article Allocation random: sealed envelope technique; exact method unclear Allocation concealment: unclear Baseline comparison: yes Baseline similarity: yes Blinding of care givers: yes Additional features to blind fluid administered: unclear Control of co-interventions: yes Completeness of follow-up: unclear Intention-to-treat analysis: unclear
Participants	Location: London, UK Centre: single centre, teaching hospital Language: English

Sinclair 1997 (*Continued*)

	Inclusion criteria: adult patients with fractures of the femoral neck Exclusion criteria: age < 55 years, fracture secondary to neoplasm, fractures occurring during hospitalization for acute illness, fracture through the site of a previous surgical correction or associated with instability of a previous prosthesis, planned regional anaesthesia (this would preclude the planned intervention) Age: mean 75 years, range 69 to 82 years Number randomly assigned: 40 (20 protocol; 20 control) Number completed study: 40 (including 2 control and 1 protocol participant deaths) ASA grade: median 2, interquartile range 2 to 3 Surgery type: dynamic hip screw (± plate): protocol 8, control 10; AO cannulated screw: protocol 4, control 3; arthroplasty: protocol 8, control 7
Interventions	Control group: GA plus conventional intraoperative fluid replacement. Oesophageal Doppler monitoring of fluid given and cardiovascular variables Protocol group: as control plus protocol-guided colloid fluid challenges monitored by oesophageal Doppler ultrasonography to optimize cardiac stroke volume
Outcomes	All-cause in-hospital mortality Length of stay: acute stay, total stay and time until medically fit for discharge Change in intraoperative physiological parameters: stroke volume, corrected flow time, cardiac output, fluid per minute of surgery
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of randomization process given
Allocation concealment (selection bias)	Unclear risk	Not clear whether sequentially numbered, opaque, sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Anaesthetist blinded to Doppler measurements but aware of fluid challenges and therefore likely to know the allocation - probably the surgeon as well. Other medical and nursing staff unaware of randomization of participant
Blinding of outcome assessment (detection bias) Mortality / adverse outcomes	Low risk	Medical and nursing staff unaware of randomization of participant
Blinding of outcome assessment (detection bias) Length of stay	Low risk	No discharge criteria given but staff were blinded, therefore unlikely to bias results

Sinclair 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers in each group included in results unclear. No details about losses to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported but length of stay reported in chart as median and IQR
Other bias	Low risk	Study groups similar at baseline

Venn 2002

Methods	Publication type: full article Allocation random: into 3 groups using computer-generated random numbers and opaque sealed envelope technique Allocation concealment: unclear Baseline comparison: yes Baseline similarity: yes Blinding of care givers: unclear Additional features to blind fluid administered: unclear about surgeon Control of co-interventions: yes Completeness of follow-up: yes Intention-to-treat analysis: used
Participants	Location: London, UK Centre: single centre, teaching hospital Language: English Inclusion criteria: adult patients undergoing repair of PFF under general anaesthesia Exclusion criteria: age < 65 years, fracture secondary to neoplasm, oesophageal pathology, patients with central venous cannula in situ, planned regional anaesthesia (this would preclude one of the planned interventions) Age: 65 to 102 ASA grade: median 3, interquartile range 3 to 4 Sugery type: dynamic hip screw/arthroplasty/AO screw: control 11/17/1; CVP 21/9/0; oesophageal Doppler 13/14/3
Interventions	Control group: GA and conventional intraoperative fluid management CVP group: GA and conventional fluid management plus intraoperative fluid challenges guided by central venous pressure, as per protocol Oesophageal doppler group: GA and conventional fluid management plus fluid challenges guided by oesophageal Doppler measurements, as per protocol
Outcomes	Postoperative complications Intraoperative hypotension Postoperative morbidity In-hospital all-cause mortality Time to medical fitness for discharge Length of hospital stay Difference in intraoperative CVP measurements (not including Doppler group)

Venn 2002 (*Continued*)

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not clear whether sequentially numbered, opaque, sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Anaesthetist (& surgeon) aware of fluid challenges and allocation of participant. "Postoperative management was performed by orthopaedic medical team and nursing staff who were unaware of patient's randomization"
Blinding of outcome assessment (detection bias) Mortality / adverse outcomes	Low risk	Medical and nursing staff unaware of randomization of participant
Blinding of outcome assessment (detection bias) Length of stay	Low risk	No discharge criteria given but staff were blinded, therefore unlikely to bias results
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in CVP group underwent intramedullary nailing but was included in ITT analyses. No losses to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Study groups similar at baseline

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Carson 1998	Wrong intervention- Hb targeting not fluid optimisation
Carson 2006	Wrong intervention. Study concentrates on titration of Hb levels rather than optimisation of fluid status
Choong 2000	Wrong intervention

(*Continued*)

Eneroth 2005	Wrong intervention. Both groups had identical fluid regimen intraoperatively
Gan 2002	Wrong participants- elective surgery and no orthopaedic participants
Lopes 2007	Only 1 participant in study who may have undergone PFF surgery (unclear), and they were assigned to the control group. Would not be appropriate to include such a small sample
Swanson 1998	Wrong intervention
Wilson 1999	No PFF participants (all general/vascular/urological surgery)

Characteristics of studies awaiting assessment *[ordered by study ID]*

Sandham 2003

Methods	Publication type: full article Allocation random: by computer-generated sequence Allocation concealment: sequentially numbered opaque sealed envelopes Baseline comparison: yes Baseline similarity: yes Blinding of care givers: not considered feasible by investigators Additional features to blind fluid administered: not considered feasible Control of co-interventions: not described Completeness of follow up: yes- to hospital discharge Intention-to-treat analysis: yes
Participants	Location: Canada Centre: 19 centres Language: English Inclusion criteria: adults undergoing high-risk, urgent or elective, major thoracic/abdominal/vascular/orthopaedic surgery, then ICU stay Exclusion criteria: nil specified Age: 60 years or older ASA grade: III to IV Surgery type: not specified
Interventions	PAC group: goal-directed fluid therapy, using PAC according to protocol to optimize oxygen delivery Control group: standard fluid therapy
Outcomes	In-hospital all cause mortality 6-Month mortality 12-Month mortality Length of stay Iatrogenic complications: wound infections; problems due to line insertion Cardiopulmonary complications: myocardial infarction; left ventricular failure; arrhythmia; pneumonia; pulmonary embolism

	Other complications: renal/liver insufficiency, sepsis
Notes	To date, unable to contact authors for outcome data regarding hip fracture subgroup. If these data become available, study will be included

Characteristics of ongoing studies *[ordered by study ID]*

GDHT study

Trial name or title	Goal Directed Haemodynamic Therapy for Patients With Proximal Femoral Fracture (GDHT)
Methods	Study type: interventional Allocation: randomized Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double blind (subject, outcomes assessor) Primary purpose: treatment
Participants	Location: Karolinska University Hospital, Sweden Centre: single centre Inclusion criteria: patients (men and women) age $\geq$ 70 years, scheduled for operation of proximal femoral fracture during office hours Exclusion criteria: lithium treatment; known allergy (or hypersensitivity) to lithium or to components of the medical device; weight $\leq$ 40 kg; other conditions or symptoms preventing the subject from entering the study, according to investigators' judgement; life expectancy less than 6 months; pathological fractures; not possible to insert arterial line
Interventions	Routine care group: routine perioperative fluid therapy Goal-directed haemodynamic therapy (GDHT) group: protocol guided
Outcomes	Number of participants with postoperative complications Health-related quality of life Number of complications Haemodynamic parameters
Starting date	March 2010 (study now completed, awaiting submission)
Contact information	erzsebet.bartha@karolinska.se
Notes	Study results submitted for publication August 2012 (personal communication with author)

NOTTS study

Trial name or title	Neck of Femur Optimisation Therapy- Targeted Stroke Volume (NOTTS) Study
Methods	Single-centre RCT
Participants	128 participants with acute primary hip fracture listed for spinal anaesthesia
Interventions	Stroke volume- guided intraoperative fluid management. Continuous measurement of SV recorded by a calibrated cardiac output monitor (LiDCOplus). Maintenance fluid and 250 mL colloid boluses given to achieve sustained 10% increases in stroke volume. Control group: fluid administration at the responsible (blinded) anaesthetist's discretion. The intervention terminates at the end of the surgical procedure, and postoperative fluid management is performed at the responsible anaesthetist's discretion
Outcomes	Primary outcome: length of hospital stay determined by team of blinded clinicians Secondary outcomes: number of complications and total cost of care
Starting date	01/01/2009
Contact information	Dr Iain Moppett iain.moppett@nottingham.ac.uk
Notes	Authors hope to submit manuscript early in 2013 (personal communication with author)

DATA AND ANALYSES

Comparison 1. Advanced haemodynamic monitoring vs protocol using standard measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse outcomes	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Cardiopulmonary	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Neurological	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Any complications, including minor	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Advanced haemodynamic monitoring vs usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	99	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.23, 4.66]

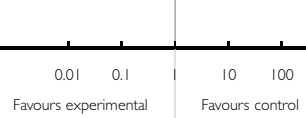
Analysis 1.1. Comparison 1 Advanced haemodynamic monitoring vs protocol using standard measures, Outcome 1 All-cause mortality.

Review: Perioperative fluid volume optimization following proximal femoral fracture

Comparison: 1 Advanced haemodynamic monitoring vs protocol using standard measures

Outcome: 1 All-cause mortality

Study or subgroup	Advanced n/N	Protocol n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Schultz 1985 (1)	1/35	10/35		0.10 [0.01, 0.74]
Venn 2002 (2)	3/30	6/31		0.52 [0.14, 1.88]



(1) Mortality time point not defined

(2) In-hospital mortality

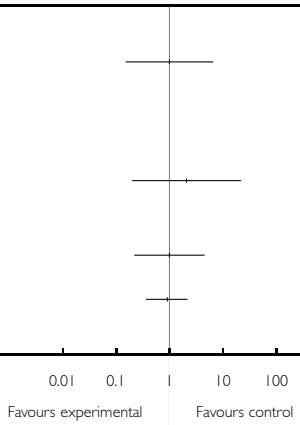
Analysis 1.2. Comparison 1 Advanced haemodynamic monitoring vs protocol using standard measures, Outcome 2 Adverse outcomes.

Review: Perioperative fluid volume optimization following proximal femoral fracture

Comparison: 1 Advanced haemodynamic monitoring vs protocol using standard measures

Outcome: 2 Adverse outcomes

Study or subgroup	Advanced n/N	Protocol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Cardiopulmonary				
Schultz 1985 (1)	2/35	2/35		1.00 [0.15, 6.71]
2 Neurological				
Schultz 1985	0/35	0/35		0.0 [0.0, 0.0]
Venn 2002 (2)	2/30	1/31		2.07 [0.20, 21.61]
3 Any complications, including minor				
Schultz 1985	3/35	3/35		1.00 [0.22, 4.62]
Venn 2002 (3)	7/30	8/31		0.90 [0.37, 2.18]



(1) 2 cases of pneumonia/pneumonitis in each group

(2) patients suffering CVA event.

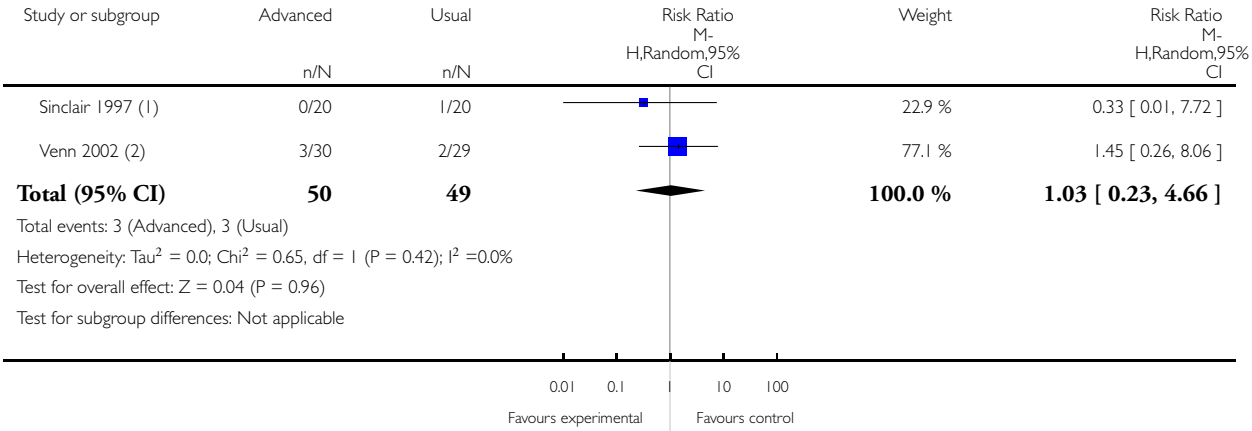
(3) Number of patients with any complication

Analysis 2.1. Comparison 2 Advanced haemodynamic monitoring vs usual care, Outcome 1 All-cause mortality.

Review: Perioperative fluid volume optimization following proximal femoral fracture

Comparison: 2 Advanced haemodynamic monitoring vs usual care

Outcome: 1 All-cause mortality



(1) 30 day mortality. Two patients who died after 30 days not included (one from each group).

(2) In-hospital mortality

ADDITIONAL TABLES

Table 1. Outcome data from Venn 2002: comparison 1

Outcomes reported in Venn 2002: comparison 1	**Advanced haemodynamic- Doppler N = 30**		**Protocol-CVP N = 31**		**Effect estimate** (95% CI)
	Mean	SD	Mean	SD	Mean difference
Length of hospital stay (days)	13.5	8.8	13.3	12.1	0.20 (-5.10 to 5.50)
Time to fitness to discharge	7.7	8.6	10	5.3	-2.30 (-5.90 to 1.30)
	Events		Events		MH relative risk
Mortality	3		6		0.52 (0.14 to 1.88)

Table 1. Outcome data from Venn 2002: comparison 1 (*Continued*)

Adverse events					
· Cardiopulmonary- episodes	6		6		N/A
· Neurological - participants	2		1		2.07 (0.20 to 21.61)
· Any, including minor- participants	7		8		0.90 (0.37 to 2.18)

Table 2. Outcome data from Venn 2002: comparison 2

Outcomes reported in Venn 2002: comparison 2	**Advanced haemodynamic- Doppler N = 30**		**Standard care N = 29**		**Effect estimate** (95% CI)
	Mean	SD	Mean	SD	Mean difference
Length of hospital stay (days)	13.5	8.8	17.5	13.8	-4.00 (-9.93 to 1.93)
Time to fitness to discharge	7.7	8.6	13.9	6.6	-6.20 (-10.10 to -2.30)
	Events		Events		MH relative risk
Mortality	3		2		1.45 (0.26 to 8.06)
Adverse events					
· Cardiopulmonary- episodes	6		7		N/A
· Neurological - participants	2		1		1.93 (0.19 to 20.18)
· Any, including minor- participants	7		14		0.48 (0.23 to 1.02)

Table 3. Length of stay data from Sinclair 1997: comparison 2

Time to medical fitness for discharge (days)		
	Control group (18 participants)	Advanced haemodynamic monitoring group (19 participants)
Extremes	6 to 125	4 to 26
Quartiles	10 to 32	8 to 10
Median	15	10
Total hospital stay		
	Control group (18 participants)	Advanced haemodynamic monitoring group (19 participants)
Extremes	5 to 220	4 to 24
Quartiles	10 to 33	8 to 15
Median	20	12

Values visually estimated by box-and-whisker plots in published trial.

Table 4. Outcome data from Venn 2002: comparison 3

Outcomes reported in Venn 2002: comparison 3	**Protocol-CVP N = 31**		**Standard care N = 29**		**Effect estimate** (95% CI)
	Mean	SD	Mean	SD	Mean difference
Length of hospital stay (days)	13.3	12.1	17.5	13.8	-4.20 (-11.0 to 2.60)
Time to fitness to discharge	10	5.3	13.9	6.6	-3.90 (-7.05 to -0.75)
	Events		Events		MH relative risk
Mortality	6		2		2.81 (0.61 to 12.81)
Adverse events					

Table 4. Outcome data from Venn 2002: comparison 3 (*Continued*)

· Cardiopulmonary episodes	6		7		N/A
· Neurological participants	1		1		0.94 (0.06 to 14.27)
· Any, including minor participants	8		14		0.53 (0.26 to 1.08)

APPENDICES

Appendix 1. CENTRAL search strategy

Search strategy used for databases

ID	Search run on CENTRAL 23/4/12
#1	MeSH descriptor Clinical Protocols explode all trees
#2	MeSH descriptor Water-Electrolyte Balance explode all trees
#3	MeSH descriptor Fluid Therapy explode all trees
#4	MeSH descriptor Infusions, Intravenous explode all trees
#5	MeSH descriptor Catheterization, Central Venous explode all trees
#6	MeSH descriptor Catheterization, Swan-Ganz explode all trees
#7	MeSH descriptor Axillary Vein explode all trees
#8	MeSH descriptor Echocardiography explode all trees
#9	MeSH descriptor Pulmonary Wedge Pressure explode all trees
#10	MeSH descriptor Critical Care, this term only
#11	MeSH descriptor Cardiac Output explode all trees
#12	MeSH descriptor Monitoring, Physiologic explode all trees

(*Continued*)

#13	(Hemodynamic* or Hemodynamic* or (critical near care) or (cardiac near output*) or (fluid near therap*) or (Electrolyte near Balance) or (infusion* near intravenous) or (fluid near volume)) or (fluid volume optimizat*) or (fluid volume optimisat*)
#14	(oesophageal or esophageal) near doppler
#15	(pulse contour analysis) or lidco or picco
#16	(Clinical Protocols) or (Water Electrolyte Balance) or (Fluid Therapy) or (Infusions Intravenous) or (Catheterization Central Venous) or (Catheterization Swan Ganz) or (Axillary Vein) or Echocardiography or (Pulmonary Wedge Pressure) or (Critical Care) or (Cardiac Output) or (Monitoring Physiologic) or (goal near directed near therapy)
#17	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18	MeSH descriptor Femoral Fractures explode all trees
#19	MeSH descriptor Femoral Neck Fractures explode all trees
#20	MeSH descriptor Hip Fractures explode all trees
#21	(fract* near (femor* or neck or hip))
#22	(#18 OR #19 OR #20 OR #21)
#23	(#17 AND #22)

Appendix 2. MEDLINE search strategy

	Search run on MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present **on 23/4/12**
1	exp Clinical Protocols/ or exp Water Electrolyte Balance/ or exp Fluid Therapy/ or exp Infusions Intravenous/ or exp Catheterization Central Venous/ or exp Catheterization Swan Ganz/ or exp Axillary Vein/ or exp Echocardiography/ or exp Pulmonary Wedge Pressure/ or Critical Care/ or exp Cardiac Output/ or exp Monitoring Physiologic/
2	(Hemodynamic* or haemodynamic* or (critical adj3 care) or (cardiac adj3 output*) or (fluid adj3 therap*) or (electrolyte adj3 balance) or (infusion* adj3 intravenous) or (fluid adj3 volume)).mp
3	(fluid volume optimizat* or fluid volume optimisat*) or (goal adj3 directed adj3 therapy).mp
4	((oesophageal or esophageal) adj3 doppler).mp.
5	(pulse contour analysis or lidco or picco).mp.

(*Continued*)

6	exp Femoral fractures/ or exp Hip Fractures/ or exp Femoral Neck Fractures/
8	(fract* adj6 (femor* or neck or hip)).mp.
9	or/1-5
10	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh
11	(Clinical Protocols or Water Electrolyte Balance or Fluid Therapy or Infusions Intravenous or Catheterization Central Venous or Catheterization Swan Ganz or Axillary Vein or Echocardiography or Pulmonary Wedge Pressure or Critical Care or Cardiac Output or Monitoring Physiologic).mp
12	11 or 9
14	12 and (8 or 6)
15	14 and 10

Appendix 3. EMBASE search strategy

	Search run on Embase **1974 to 2012 April 20 on 23/4/12**
1	exp Femoral fractures/ or exp Hip Fractures/ or exp Femoral Neck Fractures/
2	(fract* adj6 (femor* or neck or hip)).mp.
3	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab. or placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab.) not (animals not (humans and animals)).sh
4	exp clinical protocol/
5	exp electrolyte balance/
6	exp fluid therapy/
7	exp intravenous drug administration/
8	exp central venous catheterization/
9	exp swan ganz catheter/
10	exp axillary vein/

(*Continued*)

11	exp echocardiography/
12	exp lung wedge pressure/
13	intensive care/
14	exp heart output/
15	exp monitoring/
17	(clinical protocol or electrolyte balance or fluid therapy or intravenous drug administration or central venous catheterization or swan ganz catheter or axillary vein or echocardiography or lung wedge pressure or intensive care or heart output or monitoring) .mp
18	(Hemodynamic* or haemodynamic* or (critical adj3 care) or (cardiac adj3 output*) or (fluid adj3 therap*) or (electrolyte adj3 balance) or (infusion* adj3 intravenous) or (fluid adj3 volume)).mp
19	((fluid volume optimizat* or fluid volume optimisat*) or (goal adj3 directed adj3 therapy)).mp
20	((oesophageal or esophageal) adj3 doppler).mp.
21	(pulse contour analysis or lidco or picco).mp.
24	or/1-2
25	or /4-21
27	24 and 25 and 3

Appendix 4. ClinicalTrials.gov search strategy

Term	**Search run on:** clinicaltrials.gov on 5 April 2012
1	Fluid optimisation
2	Esophageal Doppler
3	Femoral neck fracture
4	Lidco
5	Picco
6	1 or 2 or 3 or 4 or 5

Appendix 5. WHO International Clinical Trials Registry Platform

Term	**Search run on: WHO International Clinical Trials Registry:** www.apps.who.int/trialsearchon 10 August 2012
1	Fluid optimisation
2	Fluid optimization
3	Esophageal Doppler
4	Oesophageal Doppler
5	Femoral neck fracture
6	Lidco
7	Picco
8	1 or 2 or 3 or 4 or 5 or 6 or 7

Appendix 6. Articles used for forward and backwards citation tracing

Titles used for backwards citation

- Brienza, N., et al., *Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study.* Critical Care Medicine, 2009. **37**(6): p. 2079-2090.
- Bundgaard-Nielsen, M., et al., *Monitoring of peri-operative fluid administration by individualized goal-directed therapy.* Acta Anaesthesiologica Scandinavica, 2007. **51**(3): p. 331-340.
- Dalfino, L., et al., *Haemodynamic goal-directed therapy and postoperative infections: earlier is better. a systematic review and meta-analysis.* Critical Care, 2011. **15**(3).
- Giglio, M.T., et al., *Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials.* British Journal of Anaesthesia, 2009. **103**(5): p. 637-646.
- Grocott, M.P.W., M.G. Mythen, and T.J. Gan, *Perioperative fluid management and clinical outcomes in adults.* Anesthesia and Analgesia, 2005. **100**(4): p. 1093-1106.
- Guest, J.F., et al., *A cost analysis of a treatment policy of a deliberate perioperative increase in oxygen delivery in high risk surgical patients.* Intensive Care Medicine, 1997. **23**(1): p. 85-90.
- Hamilton, M.A., M. Cecconi, and A. Rhodes, *A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients.* Anesthesia and Analgesia, 2011. **112**(6): p. 1392-1402.
- Kern, J.W. and W.C. Shoemaker, *Meta-analysis of hemodynamic optimization in high-risk patients.* Critical Care Medicine, 2002. **30**(8): p. 1686-1692.
- Kirov, M.Y., V.V. Kuzkov, and Z. Molnar, *Perioperative haemodynamic therapy.* Current Opinion in Critical Care, 2010. **16**(4): p. 384-392.
- Mowatt, G., et al., *Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.* Health Technology Assessment, 2009. **13**(7): p. 1-+.
- Phan, T.D., et al., *Improving perioperative outcomes: fluid optimization with the esophageal Doppler monitor, a metaanalysis and review.* Journal of the American College of Surgeons, 2008. **207**(6): p. 935-41.
- Poeze, M., J.W.M. Greve, and G. Ramsay, *Meta-analysis of hemodynamic optimization: relationship to methodological quality.* Critical Care, 2005. **9**(6): p. R771-R779.

• Rhodes, A., et al., *Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study.* Intensive Care Medicine, 2010. **36**(8): p. 1327-1332.
• Spahn, D.R. and P.G. Chassot, *CON: Fluid restriction for cardiac patients during major noncardiac surgery should be replaced by goal-directed intravascular fluid administration.* Anesthesia and Analgesia, 2006. **102**(2): p. 344-6.

Titles used for forward citation

• Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture. BMJ 1997;315:909-12
• Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P. Rondomized controlled trial to investigate influence of fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. British Journal of Anaesthesia 2002;88:65-71.
• Gan T, Soppitt A, Maroof M, el-Moalem H, Robertosn K, Moretti E et al. Goal-directed intraoperative fluid administration reduces the length of hospital stay after major surgery. Anesthesiology 2002;97:820-6.
• Schultz R, Whitfield G, Lamura J, Raciti A, Krishnamurthy S. The role of physiologic monitoring in patients with fractures of the hip. Journal of Trauma 1985;25:309-16.

Appendix 7. Study eligibility and data extraction form

General information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Report title *(title of paper/abstract/report that data are extracted from)*	
Report ID *(ID for this paper/abstract/report)*	
Study ID *(surname of first author and year first full report of study was published, e.g. Smith 2001)*	
Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*	

Study eligibility

Study characteristics	Eligibility criteria *(insert eligibility criteria for each characteristic as defined in the protocol)*	Yes/No/Unclear	Details of outcomes & location in text
Type of study	Randomized controlled trial		
	Controlled clinical trial *(quasi-randomized trial & cluster-randomized)*		
	Cross-over trial *(both interventions in patients - order randomized)*		
Participants	Adults with proximal femoral fracture who underwent surgical treatment of any type under regional or general anaesthesia		
Types of interventions and comparison	**Comparison of two or more of:**		
	Advanced invasive haemodynamic monitoring such as transoesophageal Doppler, pulse contour analysis		
	Protocol using readily available parameters such as blood pressure, urine output, central venous pressure		
	Usual care		
Outcomes	Mortality		
	Complications		
Outcomes are not part of the eligibility criteria- so a study that meets design, participant and intervention criteria is included.			
INCLUDE EXCLUDE UNCLEAR			
Reason for exclusion:			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Population and setting

	Description	Location in text
Population description *(types of surgical procedures included)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Informed consent obtained		

Methods

	Descriptions as stated in report/paper	Location in text
Aim of study		
Design *(e.g. parallel, crossover, cluster)*		
Unit of allocation *(by individuals, cluster/ groups or body parts)*		
Start date		
End date		
Total study duration		
Ethical approval needed/ obtained for study		

Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text
Total no. randomized *(or total pop. at start of study for NRCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Race/Ethnicity		
Type and duration of surgery *(Method of fracture fixation)*		
Details of anaesthetic given *(GA or regional, sedation, neuromuscular blockade used, any specific details)*		
Seniority of anaesthetist		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		

Intervention groups

Intervention group- repeated as required

	Description as stated in report/paper	Location in text
Group name *(advanced monitoring, protocol, or usual care)*	First or second generation SAD	
Specific monitoring used *(Inc detail of protocols)*		
No. randomized to group		

Comparison group

	Description as stated in report/paper	Location in text
Group name *(advanced monitoring, protocol, or usual care)*	Tracheal tube	
Specific monitoring used *(Inc detail of protocols)*		
No. randomized to group		

Outcomes

For each outcome ticked, please complete a separate outcome form.

	Description as stated in report/paper	Location in text
Outcome name *(number of attempts, pain)*		
Time points measured		

(*Continued*)

Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Scales: levels, upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*		
Power		
RESULTS	**Description as stated in report/paper**	**Location in text**
Comparison		
Outcome		
Subgroup		
Timepoint *(specify whether from start or end of intervention)*		
Postintervention or change from baseline?		
Results: Intervention*		
Results: Comparison*		
No. missing participants and reasons		

(*Continued*)

No. participants moved from other group and reasons		
Any other results reported		
Unit of analysis *(individuals, cluster/ groups or body parts)*		
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*		
Reanalysis required? *(specify)*		
Reanalysed results		

*Results for continuous outcome: mean: SD (or other variance): total number of participants.
Results for dichotomous outcome: number participants with outcome: total number of participants.

Risk of bias assessment

Domain	Risk of bias : high/low /unclear	Support for judgement	Location in text
Random sequence generation *(selection bias)*			
Allocation concealment *(selection bias)*			
Blinding of participants and personnel *(performance bias)*			
Blinding of outcome assessment *(detection bias)*			
Incomplete outcome data *(attrition bias)*			

(*Continued*)

Selective outcome reporting? *(reporting bias)*			
Other bias *(baseline characteristics for cluster-randomized, carryover for crossover trials)*			

Applicability

	Yes/No/Unclear	Support for judgement
Have important populations been excluded from the study? *(consider disadvantaged populations and possible differences in the intervention effect)*		
Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*		
Does the study directly address the review question? *(any issues of partial or indirect applicability)*		

Other information

	Description as stated in report/paper	Location in text
Key conclusions of study authors		
References to other relevant studies		

(*Continued*)

Correspondence required for further study information *(from whom, what and when)*	

WHAT'S NEW

Last assessed as up-to-date: 19 October 2012.

Date	Event	Description
9 September 2013	New search has been performed	• We amended the search strategy and re-ran the search from inception of the databases to October 2012. We repeated title selection and full text review in full. • We moved one study from excluded to included studies (Schultz 1985). One study was added as awaiting classification pending contact with authors (Sandham 2003). We added two ongoing studies (GDHT study; NOTTS study). • We included 'Summary of findings' tables for each comparison. • We used the Cochrane 'Risk of bias' tool to assess the quality of studies. We did not exclude studies on the basis of low quality. • We redefined outcomes to separate length of stay into time to medical fitness and total stay. The all-cause mortality time frame was changed to include in-hospital, 30 days and undefined. Reduced return of function outcomes were changed to time to the pre-fracture category of accommodation and mobility. We reclassified complications into major iatrogenic, cardiopulmonary, neurological and combined, including minor. • We altered comparison groups so that protocol measures and advanced haemodynamic methods were not combined and were compared with each other.
9 September 2013	New citation required but conclusions have not changed	The previous authors (Price 2004) decided not to update this review. New authors have updated this version. No change has been made to the conclusions

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 1, 2002

Date	Event	Description
16 January 2008	Amended	Converted to new review format.
10 November 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AFS identified the need for the review update.

AB and AN developed the update, with refinements by MT and AFS.

AB and AN performed the initial searches, applied inclusion criteria and extracted study data.

AB and AN compiled the results and drafted the review.

All authors reviewed and refined the final manuscript.

DECLARATIONS OF INTEREST

AB, AFS, MT: none declared.

AN: From March to August 2011, AN worked for the Cardiff Research Consortium, which provides research and consultancy services to the pharmaceutical industry. Cardiff Research Consortium has no connection with AN's work with The Cochrane Collaboration. AN's husband has small direct holdings in several drug and biotech companies as part of a wider balanced share portfolio.

SOURCES OF SUPPORT

Internal sources

- Oxford Radcliffe Hospitals NHS Trust, UK.

External sources

- NIHR Cochrane Collaboration Programme Grant, UK.
- NIHR Cochrane Collaboration Programme Grant. Enhancing the safety, quality and productivity of perioperative care. Project Ref: 10/4001/04, UK This grant funds the work of AN and AJS on this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We altered and re-ran the search strategy using updated key terms from the inception of the databases to October 2012. In addition to CENTRAL, MEDLINE and EMBASE, we searched the International Clinical Trials Registry Platform and ClinicalTrials.gov Websites for ongoing and unpublished studies (see Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5). We carried out backward and forward citation searching for key review articles identified during the initial searches (see Appendix 6). We repeated title selection and full text review in full.

We moved one study from excluded to included studies (Schultz 1985). One study was added as awaiting classification pending contact with authors (Sandham 2003). We added two ongoing studies (GDHT study; NOTTS study).

We used the Cochrane 'Risk of bias' tool to assess the quality of studies. We did not exclude studies on the basis of low quality.

We altered comparison groups so that protocol measures and advanced haemodynamic methods were compared with each other and were not combined.

We redefined outcomes to separate length of stay into time to medical fitness and total stay. The all-cause mortality time frame was changed to included in-hospital, 30 days and undefined. Reduced return of function outcomes was changed to time to the pre-fracture category of accommodation and mobility. We reclassified complications into major iatrogenic, cardiopulmonary, neurological and combined, including minor.

We included summary of findings tables for each comparison, using the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Femoral Fractures [therapy]; Fluid Therapy [*methods]; Hip Fractures [complications; *surgery]; Hypovolemia [complications; *therapy]; Length of Stay; Randomized Controlled Trials as Topic

MeSH check words

Humans