National Institute for Health and Care Excellence

Final

Perioperative care in adults

[I] Evidence review for intravenous fluid management strategy

NICE guideline NG180

Evidence reviews underpinning recommendations 1.4.3 and 1.4.4 in the NICE guideline

August 2020

Final

This evidence review was developed by the National Guideline Centre

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Contents

1 Intravenous fluid management strategy

1.1 Review question: What is the most clinically and cost-effective type of intraoperative intravenous fluid for adults undergoing surgery?

1.2 Introduction

The type of fluid administered in the perioperative period can have a significant effect on outcomes in patients have major surgery. There has been considerable debate over the safety and efficacy of crystalloids versus colloids. The key difference between crystalloids and colloids is that the colloids contain much larger molecules than that of crystalloids. Crystalloids are aqueous solutions of salts, minerals or any other water-soluble substances, for example, saline. Colloid solutions include hetastarch, dextran and plasma protein solutions. Since they are remaining in the vascular system, colloids are much more effective to use for expanding the circulatory volume than crystalloids. However, excessive use of colloids has been associated with side effects such as peripheral and pulmonary oedema and cardiac failure.

Recent evidence has been identified to address the question on the clinical and cost effectiveness of crystalloids versus colloids. The aim of this review is to perform a systematic review collating all of the relevant evidence.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults 18 years and over having surgery.

Interventions	• Crystalloid:
	  ○ plasma, sodium chloride 0.9% (normal saline); sodium chloride 0.18%/4% glucose; 0.45% sodium chloride/4% glucose; 5% glucose; Hartmann's; Lactated Ringer's (USP); Ringer's acetate; Plasmalyte
	• Colloid
	  ○ gelatines; starches; albumin

Comparisons	• To each other • A within class comparison will be undertaken for the class that is found to be more effective.
Outcomes	Critical outcomes: • health-related quality of life • mortality • adverse events and complications (Clavien-Dindo; postoperative morbidity score (POMS); acute kidney injury; coagulopathy; nausea and vomiting; pulmonary complications, surgical site infections) Important outcomes: • length of hospital stay • unplanned ICU admission • ICU length of stay (planned and unplanned)

Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.

1.4 Clinical evidence

1.4.1 Included studies

Thirteen randomised controlled trials were included in the review;[1, 18, 22, 23, 40, 57, 69, 70, 74, 83, 84, 87, 89] these are summarised in Table 2 and 3 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 4).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review (primary analysis)

Study	Intervention and comparison	Population	Outcomes	Comments
Abdallah 2014[1]	**Crystalloid:** Intraoperative intravenous infusion of 0.9 % normal saline alone. N=22 **Colloid:** Intraoperative intravenous infusion of 20 % human albumin with 0.9 % normal saline. N=22	Patients with end-stage renal disease undergoing kidney transplantation. Mean age (SD): 54.35 years (11.5) Egypt	• Complications: ○ Pulmonary	Colloid group received infusion of crystalloid and colloid.
Farag 2012[22]	**Crystalloid:** Additional lactated Ringer's solution was given intraoperatively as guided by oesophageal Doppler. N=29 **Colloid:** 5% human albumin was given as guided by oesophageal Doppler to supplement maintenance crystalloid. N=31	Patients scheduled for complex spine surgery in prone position. Mean age (SD): 58.5 (11.5) USA	• Length of hospital stay • Length of ICU stay	All the patients were given 5–7 ml/kg lactated Ringer's solution in the immediate preoperative period, which was followed by 6–7 ml/kg/h lactated Ringer's solution for maintenance.
Feldheiser 2013[23]	**Crystalloid:** Received balanced crystalloid (Jonosteril) solution up to the dose limit (50 ml kg21).	Patients with primary ovarian cancer undergoing cytoreductive surgery.	• Mortality • Complication • Length of hospital stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	Administered measured by oesophageal Doppler within a goal-directed haemodynamic algorithm. N=24 **Colloid:** Balanced starch ((Volulyte, HES, 130/0.4, 6%) solutions up to the dose limit (50 ml kg^{-1}). Administered measured by oesophageal Doppler within a goal-directed haemodynamic algorithm. N=26	Germany	• Length of ICU stay	

Joosten 2018[40]	**Crystalloid:**
	A closed-loop system delivered additional 100-ml crystalloid (Plasmalyte) boluses according to a predefined goal-directed strategy.
	N=80
	
	Colloid:
	A closed-loop system delivered additional 100-ml colloid (Volulyte) boluses according to a predefined goal-directed strategy.
	N=80
		Adult patients scheduled to undergo general anaesthesia for elective open abdominal surgery expected to last at least 3 hours.
		
		Age range: 48-73 years
		
		Belgium
			• Mortality
			• Complications:
			  ○ Major complication
			  ○ AKI
			  ○ Nausea and vomiting
			  ○ Pulmonary
			  ○ Wound infection
			• Length of hospital stay
			• Length of ICU stay
				All patients had maintenance-balanced crystalloid administration of 3 $ml/kg^{-1}/ h^{-1}$

Moretti 2003[57]	**Crystalloid:** Patients received lactated Ringer's solution for the treatment of hypovolemia	ASA physical status I–III adult patients presenting for major elective general, gynaecological, orthopaedic,	• Complications: ○ Nausea	Before the induction of anaesthesia, all patients received an IV bolus of 7 mL/kg of LR solution was administered

Study	Intervention and comparison	Population	Outcomes	Comments
	according to a hypovolemia algorithm. N=30 **Colloid:** Patients received either 6% hetastarch in saline or Hextendt for the treatment of hypovolemia according to a hypovolemia algorithm. N=60	or urologic surgery with an anticipated blood loss of >500 mL. Mean age: 59 years USA		followed by an IV infusion of LR solution at a rate of 5 mL/kg^{1} /h^{1} throughout surgery.
Shah 2014[70]	**Crystalloid:** Intraoperative fluid regimen of 0.9% normal saline. N=40 **Colloid:** Intraoperative fluid regimen of 0.9% normal saline with 20% human albumin. N=40	Patients undergoing renal transplantation. Mean age (SD): 33.4 years (10) India	• Complications: ○ Pulmonary	Crystalloid vs crystalloid + colloid At the end of surgery, the study fluid was discontinued and all the patients received an infusion of dextrose 5%/0.45% normal saline at rate of 50 mL/hour.
Szturz 2014[74]	**Crystalloid:** Intraoperative hemodynamic optimization (fluid therapy with Ringer's and administration of vasoactive drugs) was started according to TED variables to maintain cardiac index between 2.6 and 3.8 l/min/m^{2} N=57 **Colloid:** Intraoperative hemodynamic optimization (fluid therapy with	Consecutive patients undergoing elective major urological surgery. Age range: 22-93 years Czech republic	• Mortality • Complications • Length of hospital stay • Length of ICU stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	hydroxyethyl starch 6 % 130/0.4 and administration of vasoactive drugs) was started according to TED variables to maintain cardiac index between 2.6 and 3.8 l/min/m^2 N=58			
Werner 2018[84]	**Crystalloid:** Balanced crystalloid solution according to a goal-directed hemodynamic algorithm guided by the oesophageal Doppler monitor. N=21 **Colloid:** Hyperoncotic balanced 10% HES 130/0.42 solution according to a goal-directed hemodynamic algorithm guided by the oesophageal Doppler monitor. N=20 **Colloid:** Isotoncotic balanced 6% HES 130/0.42 solution according to a goal-directed hemodynamic algorithm guided by the oesophageal Doppler monitor. N=22	Patients scheduled for elective surgery of the pancreatic head due to primary pancreatic cancer or chronic pancreatitis. Age range: 50-72 years Germany	• Complications: ○ AKI	
Yates 2014[87]	**Crystalloid:** Balanced crystalloid	Medium to high-risk patients undergoing elective	• Mortality • Complications	All patients received an i.v. infusion of Hartmann's solution at

Study	Intervention and comparison	Population	Outcomes	Comments
	(Hartmann's solution) as haemodynamic optimization fluid. N=98 **Colloid:** Balanced 6% HES (130/0.4, Volulyte) as haemodynamic optimization fluid. N=104	colorectal surgery. Age range: 56-88 years UK	• Length of hospital stay	a rate of 1.5 ml kg^{-1} h^{-1} from the start of the trial period and this continued for 24 h.

Zhang 2012[89]	**Crystalloid:**
	The goal-directed Ringer's lactate group received a fixed infusion of 4 ml/kg per hour of lactated Ringer's solution throughout the operation. In addition, this group received 250 ml of lactated Ringer's solution as a bolus in 15 minutes if the PPV was >11%.
	N=20
	
	Colloid:
	The goal-directed colloid group received a fixed infusion of 4 ml/kg per hour of lactated Ringer's solution throughout the operation. In addition, this group received 250 ml of 6% hydroxyethyl starch (HES, 130/0.4) as a bolus in 15 minutes if the PPV was >11%.
	N=20
		Patients who were undergoing gastrointestinal surgery.
		
		Mean age (SD): 54.3 years (10.6)
		
		China
			• Complications:
			  ○ Vomiting
			  ○ Pulmonary
			  ○ SSI
			• Length of hospital stay
				Goal directed crystalloid arm included for analysis

Table 3: Summary of studies included in the evidence review (secondary analysis)

Study	Intervention and comparison	Population	Outcomes	Comments
Dawidson 1991[18]	Crystalloid: Lactated Ringers with dextran-60 during surgery and 24 hours post-operatively. N=10 Crystalloid: Lactated Ringers during surgery and 24 hours post-operatively. N=10	Consecutive patients undergoing abdominal aortic surgery.	• Mortality • Length of hospital stay	
Shackford 1983[69]	Crystalloid: Lactated Ringers, 130 mEq sodium/L, 274 mOsm/L) N=28 Crystalloid: Hypertonic balanced salt solution (HSL, 205 mEq sodium/L, 514 mOsm/L). N=30	Patients undergoing abdominal aortic reconstruction. Mean age (SD): 61 years (1.5) USA	• Mortality • Complications: Pulmonary • Complication: Renal failure	
Waters 2001[83]	Crystalloid: Intraoperative Lactated ringers. Anaesthetic and fluid management were standardised. N=33 Crystalloid: Intraoperative normal saline. Anaesthetic and fluid management were standardised. N=33	Patients undergoing aortic reconstructive surgery. Mean age (SD): 70 years (8) USA	• Mortality • Infection (sepsis)	

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 4: Clinical evidence summary: Crystalloid versus colloid

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with colloid	Risk difference with crystalloid (95% CI)
Mortality (1 to 3 months)	410 (3 studies) 1-3 months	⨁⊖⊖⊖ VERY LOW1,2 due to inconsistency, imprecision	RR 0.59 (0.07 to 4.81)	Moderate	
				48 per 1000	20 fewer per 1000 (from 45 fewer to 183 more)
Complication: (patients with major complication)	362 (2 studies)	⨁⊖⊖⊖ VERY LOW1,2 due to inconsistency, imprecision	RR 1.37 (0.43 to 4.44)	Moderate	
				181 per 1000	67 more per 1000 (from 103 fewer to 623 more)
Complication: Acute kidney injury	212 (2 studies)	⨁⨁⊖⊖ LOW2 due to imprecision	RR 1.04 (0.75 to 1.45)	Moderate	
				494 per 1000	20 more per 1000 (from 124 fewer to 222 more)
Complication: Nausea and vomiting	290 (3 studies)	⨁⨁⨁⊖ MODERATE2 due to imprecision	RR 1.41 (1.08 to 1.85)	Moderate	
				350 per 1000	143 more per 1000 (from 28 more to 298 more)
Complication: Nausea and vomiting - Nausea and vomiting	160 (1 study)	⨁⨁⊖⊖ LOW2 due to imprecision	RR 1.18 (0.79 to 1.75)	Moderate	
				350 per 1000	63 more per 1000 (from 73 fewer to 262 more)
Complication: Nausea and vomiting - Vomiting	40 (1 study)	⨁⨁⊖⊖ LOW2 due to imprecision	RR 1.67 (0.46 to 6.06)	Moderate	
				150 per 1000	100 more per 1000 (from 81 fewer to 759 more)
Complication: Nausea and vomiting - Nausea	90 (1 study)	⨁⨁⨁⊖ MODERATE2 due to imprecision	RR 1.76 (1.22 to 2.55)	Moderate	
				417 per 1000	317 more per 1000 (from 92 more to 646 more)
Complication: Pulmonary	526	⨁⊖⊖⊖	RR 1.57	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with colloid	Risk difference with crystalloid (95% CI)
	(5 studies)	VERY LOW1 due to inconsistency, imprecision	(0.56 to 4.40)	46 per 1000	9 more per 1000 (from 12 fewer to 44 more)
Complication: Wound infection	200 (2 studies)	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.17 (0.41 to 3.35)	Moderate	
				56 per 1000	26 more per 1000 (from 20 fewer to 156 more)
Complications: Clavien-Dindo grade I	48 (1 study) 3 months	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.08 (0 to 1.29)	Moderate	
				250 per 1000	230 fewer per 1000 (from 250 fewer to 72 more)
Complications: Clavien-Dindo grade II	48 (1 study) 3 months	⊕⊕⊕⊖ MODERATE2 due to imprecision	RR 1.67 (0.91 to 3.04)	Moderate	
				375 per 1000	251 more per 1000 (from 34 fewer to 765 more)
Complications: Clavien-Dindo grade IIIa	48 (1 study) 3 months	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1 (0.07 to 15.08)	Moderate	
				42 per 1000	0 fewer per 1000 (from 39 fewer to 591 more)
Complications: Clavien-Dindo grade IIIb	48 (1 study) 3 months	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.6 (0.16 to 2.23)	Moderate	
				208 per 1000	83 fewer per 1000 (from 175 fewer to 256 more)
Complications: Clavien-Dindo grade IVa	48 (1 study) 3 months	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.2 (0.01 to 3.96)	Moderate	
				83 per 1000	66 fewer per 1000 (from 82 fewer to 246 more)
Length of hospital stay	40 (1 study)	⊕⊕⊕⊕ HIGH		The mean length of hospital stay in the control groups was 9.1 days	The mean length of hospital stay in the intervention groups was 2.8 higher (1.99 to 3.61 higher)

1 Downgraded by 1 or 2 increments because heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 5: Evidence not suitable for GRADE analysis: Crystalloid versus colloid

Outcome	Study (no. of participants)	Risk of bias	Crystalloid results	Colloid results	*P* value
Mortality	Szturz 2014[74] (97)	High	Mortality was not significantly different between groups.		n/a
Quality of life (EQ-5D)	Feldheiser 2013[23] (48)	High	Part 1 median (25%-75%): 2.5 (0.3-4)	Part 1 median (25%-75%): 2 (2-3.8)	0.864
			Part 2 median (25%-75%): 60 (42-80)	Part 2 median (25%-75%): 50 (46-74)	0.72
Complications	Szturz 2014[74] (97)	High	Number of complications (hemodynamic, respiratory, renal, GIT, coagulation and neurology) did not reach statistical significance during ICU hospitalization. There was a statistical significance related only to gastrointestinal tract dysfunction in the crystalloid group (31.6 %) versus the colloid group (15.5 %; p = 0.05).		n/a
Length of hospital stay (days)	Feldheiser 2013[23] (48)	Low	Median (25%-75%): 13.5 (12-17.9)	Median (25%-75%): 13.8 (11-16)	0.4
	Farag 2012[22] (60)	High	Median (25%-75%): 5 (4-6)	Median (25%-75%): 5 (4-7)	0.3
	Joosten 2018[40] (160)	Low	Median (25%-75%): 10 (6-16)	Median (25%-75%): 10 (6-13)	0.43
	Szturz 2014[74] (97)	High	Length of hospital stay was not significantly different between groups.		n/a
	Yates 2014[87] (202)	Low	Median: 8	Median: 9	0.74

Outcome	Study (no. of participants)	Risk of bias	Crystalloid results	Colloid results	*P* value
Length of ICU stay (hours)	Farag 2012[22] (60)	High	The mean and SE of the average of the PACU admission were similar in the albumin and lactated Ringer's solution groups.		n/a
	Feldheiser 2013[23] (48)	Low	Median (25%-75%): 18 (6-35)	Median (25%-75%): 42 (18-67)	0.08
	Joosten 2018[40] (160)	Low	Median (25%-75%): 20 (18-22)	Median (25%-75%): 20 (18-22)	0.96
	Szturz 2014[74] (97)	High	Length of ICU stay was not significantly different between groups.		n/a

Table 6: Clinical evidence summary: Lactated Ringer's compared to normal saline for perioperative care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Normal saline	Risk difference with Lactated Ringer's (95% CI)
Mortality	66 (1 study)	⨁⨁⊖⊖ LOW1 due to imprecision	RR 1 (0.07 to 15.33)	Moderate	
				30 per 1000	0 fewer per 1000 (from 28 fewer to 430 more)
Infection (sepsis)	66 (1 study)	⨁⨁⊖⊖ LOW1 due to imprecision	Peto OR 0.14 (0 to 6.82)	Moderate	
				30 per 1000	26 fewer per 1000 (from 30 fewer to 175 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 7: Clinical evidence summary: Lactated Ringer's (+ 3% dextrose) compared to Lactated Ringer's for perioperative care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lactated Ringer's	Risk difference with Lactated Ringer's (+ 3% dextrose) (95% CI)
Mortality	20 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1 (0.07 to 13.87)	Moderate	
				100 per 1000	0 fewer per 1000 (from 93 fewer to 1000 more)
Length of hospital stay	20 (1 study)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean length of hospital stay in the control groups was 17 days	The mean length of hospital stay in the intervention groups was 6 lower (15.46 lower to 3.46 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 8: Clinical evidence summary: Hypertonic balanced salt compared to Lactated Ringer's for perioperative care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lactated Ringer's	Risk difference with Hypertonic balanced salt (95% CI)
Mortality	58 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.93 (0.06 to 14.22)	Moderate	
				36 per 1000	3 fewer per 1000 (from 34 fewer to 476 more)
Complication: Pulmonary	58 (1 study)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RD 0.00 (-0.06 to 0.06)	Moderate	
				0 per 1000	-
Complication: Renal failure	58 (1 study)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RD 0 (-0.06 to 0.06)	Moderate	
				0 per 1000	-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lactated Ringer's	Risk difference with Hypertonic balanced salt (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.5.3 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 9: UK costs of intravenous fluids

Fluid	Cost of fluid	Source
Crystalloid	(2000ml)[a]	
Sodium chloride 0.9%	£1.40	NICE Guideline Intravenous fluid therapy (CG174)[60]
Sodium Chloride 0.18% and Glucose 4%	£0.82	GC member
Sodium Chloride 0.45%	£4.76	GC member
Sodium chloride 0.45% and Glucose 2.5%	£2.88	GC member
Sodium chloride 0.45% and Glucose 5%	£1.72	GC member
Sodium chloride 0.9% and Glucose 5%	£4.28	GC member
Potassium Chloride 0.3% and Glucose 5%	£1.38	GC member
Potassium Chloride 0.3% and Sodium Chloride 0.9%	£5.18	GC member
Potassium Chloride 0.15% and Glucose 5%	£1.08	GC member
Potassium Chloride 0.15% and Sodium Chloride 0.9%	£1.48	GC member
Hartmann's solution	£1.70	NICE Guideline Intravenous fluid therapy (CG174)[60]
Plasmalyte 135	£21.00	GC member
Plasma-Lyte M	£1.84	NICE Guideline Intravenous fluid therapy (CG174)[60]
Ringer's Lactate	£5.00	NICE Guideline Intravenous fluid therapy (CG174)[60]
Average cost	**£3.89**	
Colloid	(1000ml)[a]	
Gelatin	£9.31	British National Formulary, September 2019[39]
Tetrastarch	£21.26	British National Formulary, September 2019 [39]

Fluid	Cost of fluid	Source
Average	**£15.29**	

(a) The average amount of crystalloid required is approximately 2000ml whereas the average amount of colloid required is less and is approximately 1000ml; averages were estimated by the committee.

1.6 Evidence statements

1.6.1 Clinical evidence statements

No evidence was identified for unplanned ICU admission or hospital readmission.

Crystalloid versus colloid

Mortality

Three studies showed a clinically important benefit of crystalloid in mortality compared to colloid (3 studies, n=410, Very Low quality evidence).

Adverse events

Two studies showed no clinically important difference between crystalloid and colloid for the number of patients with major complications (2 studies, n=362, Very Low quality evidence).

Two studies showed no clinically important difference between crystalloid and colloid for acute kidney injury (2 studies, n=212, Low quality evidence).

Three studies showed a clinically important harm of crystalloid in nausea and vomiting compared to colloid (3 studies, n=290, Moderate quality evidence).

Five studies showed no clinically important difference between crystalloid and colloid for pulmonary complications (5 studies, n=526, Very Low quality evidence).

Two studies showed no clinically important difference between crystalloid and colloid for wound infection (2 studies, n=200, Low quality evidence).

One study showed an increase in minor complications with crystalloid but a trend towards fewer severe complications compared to colloid (1 study, n=48, Low quality evidence).

Length of hospital stay

One study found a clinically important harm of crystalloid for length of hospital stay compared to colloid (1 study, n=40, Low quality evidence).

Evidence not suitable for GRADE analysis:

One study found no notable difference between crystalloid and colloid in mortality (1 study, n=97, high risk of bias).

One study found no statistically significant difference in quality of life between crystalloid and colloid (1 study, n=50, high risk of bias).

One study found no notable difference in complications between crystalloid and colloid (1 study, n=97, high risk of bias).

Five studies showed no statistically significant difference in length of hospital stay between crystalloid and colloid (5 studies, n=567, low risk of bias).

Four studies showed no statistically significant difference in length of ICU stay between crystalloid and colloid (4 studies, n=365, high risk of bias).

Lactated Ringer's compared to normal saline

Mortality

One study showed no clinically important difference between Lactated Ringer's and normal saline for mortality (1 study, n=66, Low quality evidence)

Adverse events

One study showed no clinically important difference between Lactated Ringer's and normal saline for sepsis (1 study, n=66, Low quality evidence)

Lactated Ringer's (+ 3% dextrose) compared to Lactated Ringer's

Mortality

One study showed no clinically important difference between Lactated Ringer's (+ 3% dextrose) compared to Lactated Ringer's for mortality (1 study, n=20, Very Low quality evidence)

Length of hospital stay

One study showed no clinically important difference between Lactated Ringer's (+ 3% dextrose) and Lactated Ringer's for length of hospital stay (1 study, n=20, Low quality evidence)

Hypertonic balanced salt compared to Lactated Ringer's

Mortality

One study showed no clinically important difference between hypertonic balanced salt and Lactated Ringer's for mortality (1 study, n=58, Very Low quality evidence)

Adverse events

One study showed no clinically important difference between hypertonic balanced salt and Lactated Ringer's for pulmonary complications (1 study, n=58, Very Low quality evidence)

One study showed no clinically important difference between hypertonic balanced salt and Lactated Ringer's for renal failure (1 study, n=58, Very Low quality evidence)

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

Please see recommendations 1.4.3 – 1.4.4 in the guideline.

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The type of fluid administered in the perioperative period can have a significant effect on outcomes in patients have major surgery. As such, the committee considered critical outcomes for decision making to be health-related quality of life, mortality, adverse events and complications. The committee also considered length of hospital stay, unplanned ICU admission, ICU length of stay and hospital readmission to be important outcomes for the safety and efficacy of IV fluids.

No evidence was identified for unplanned ICU admission or hospital readmission.

1.7.1.2 The quality of the evidence

The quality of evidence that was suitable for GRADE analysis ranged from low to high. The majority of the evidence was graded at low quality. This was mostly due to imprecision of data, reducing the certainty with which the committee could make conclusions from the evidence. The committee found that the lack of high quality evidence was a limiting factor in making any strong recommendation for or against any one type of fluid based solely on the evidence presented.

1.7.1.3 Benefits and harms

The committee reviewed the evidence comparing crystalloid IV fluid to colloid IV fluid. There was an observed reduction in mortality with crystalloid, although this evidence showed high levels of inconsistency.

The committee also noted that crystalloid fluid was associated with higher rates of nausea and vomiting. The committee considered that this could be due to changes in sodium levels with crystalloid fluid management, or potentially due to tissue oedema.

The committee agreed that the evidence showed no difference between crystalloid and colloid fluid management for other complications such as pulmonary complication, or infections. The committee felt that there also was no difference seen for the outcomes of quality of life or length of hospital stay.

The committee highlighted evidence on the use of IV colloids for fluid resuscitation within the ICU and trauma setting, noting an increased risk of AKI, coagulopathy and mortality with colloid use. The committee were confident that this evidence was applicable to the perioperative setting and referred to this data to inform the recommendations.

In summary, the committee highlighted that although crystalloids were associated with a clinically important reduction in mortality compared to colloids, there were also evidence of harm with respect to nausea and vomiting. The committee were confident that colloids are associated with harms not reported in the evidence but from other patient populations. The committee therefore made a consider recommendation for crystalloids.

1.7.2 Cost effectiveness and resource use

No economic evaluations were identified for this question.

Unit costs of types of crystalloids and colloids were presented to aid consideration of cost effectiveness. There are considerable differences in the costs of crystalloids and colloids. There are different types of crystalloids available in the NHS but the average cost across 14 different types is £3.89 for 2000ml. The average cost of two different types of colloids is £15.29 for 1000ml. Current practice does not vary and most centres use crystalloids. Colloids are not as readily available in NHS because of there being a shift away from the use of colloids due to an observed risk of acute kidney injury (AKI). The committee noted that although current practice is to use crystalloids, there may be some centres still using colloids in specific situations.

The clinical review showed a reduction in mortality with crystalloids which would lead to a QALY gain with crystalloids. However, the committee acknowledged that there was a high level of inconsistency in this result and was not certain whether there would be a mortality difference in reality. The clinical review also suggested there was a clinical benefit of crystalloids in relation to minor complications (Clavien-Dindo grades 1 and 2) which may have a short-term impact on quality of life also resulting in an increase in QALYs. However, it demonstrated that crystalloids resulted in more nausea and vomiting. The committee noted that due to the lower costs and possible clinical benefit associated with crystalloids they are likely to be cost effective.

The committee acknowledged that the recommendation would not lead to a substantial resource impact as crystalloids are already used in current practice and felt that crystalloids are likely to be cost effective.

1.7.3 Other factors the committee took into account

The committee added that heta-starch (HES) was withdrawn from licence in 2011 due to this potential risk. The committee felt that having since been re-licenced, HES is more often used within research than clinical practice. Although, the committee added that there is some variation in practice with colloids still being used across the UK.

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Appendices

Appendix A: Review protocols

Table 10: Review protocol: Intravenous fluid management strategy

ID	Field	Content
0.	PROSPERO registration number	Not registered on PROSPERO
1.	Review title	What is the most clinically and cost-effective type of intraoperative intravenous fluid for adults undergoing surgery?
2.	Review question	What is the most clinically and cost-effective type of intraoperative intravenous fluid for adults undergoing surgery?
3.	Objective	To determine the most clinically and cost effective type of intraoperative intravenous fluid for adults undergoing surgery.
4.	Searches	• Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Perioperative care
6.	Population	Inclusion: Adults 18 years and over having surgery. Exclusion: • children and young people aged 17 years and younger • surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	• Crystalloid (plasma, sodium chloride 0.9% (normal saline); sodium chloride 0.18%/4% glucose; 0.45% sodium chloride/4% glucose; 5% glucose; Hartmann's; Lactated Ringer's (USP); Ringer's acetate; Plasmalyte)

8.	Comparator/Reference standard/Confounding factors	• Colloid (gelatins; starches; albumin) A within class comparison will be undertaken for the class that is found to be more effective.
9.	Types of study to be included	Randomised controlled trials (RCTs), systematic reviews of RCTs. Observational studies if no RCT evidence is identified.
10.	Other exclusion criteria	Exclusions: • non-English language studies • cross-over randomised controlled trials • studies published before 2000
11.	Context	n/a
12.	Primary outcomes (critical outcomes)	• health-related quality of life • mortality • adverse events and complications (Clavien-Dindo; postoperative morbidity score (POMS); acute kidney injury; coagulopathy; nausea and vomiting; pulmonary complications, surgical site infections) The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
13.	Secondary outcomes (important outcomes)	• length of hospital stay • unplanned ICU admission • ICU length of stay (planned and unplanned) The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic

		Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool • Cross sectional study: JBI checklist for cross sectional study • Case series: Institute of Health Economics (IHE) checklist for case series 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • CERQual will be used to synthesise data from qualitative studies. • WinBUGS will be used for network meta-analysis, if possible given the data identified. • List any other software planned to be used. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and

		visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.	
17.	Analysis of sub-groups	Subgroups: • older adults (over 60) • surgery grade based on NICE preoperative tests for elective surgery guideline categorisation • American Society of Anesthesiologists (ASA) Physical Status grade	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	[To be added.]	
22.	Anticipated completion date	[To be added.]	
23.	Stage of review at time of this submission	Review stage Preliminary searches Piloting of the study selection process Formal screening of search results against eligibility criteria Data extraction Risk of bias (quality) assessment Data analysis	
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre	
25.	Review team members	From the National Guideline Centre:	

		Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swain Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davies Ms Lina Gulhane
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	n/a
30.	Reference/URL for published protocol	n/a
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the

		guideline within NICE.	
32.	Keywords	Perioperative care, crystalloid, colloid	
33.	Details of existing review of same topic by same authors	n/a	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	n/a	
36.	Details of final publication	www.nice.org.uk	

Table 11: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[61] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

	• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. For example, economic evaluations based on observational studies will be excluded, when the clinical review is only looking for RCTs,

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2018.[61]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 30 May 2019	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 30 May 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	Intraoperative Care/ or exp Intraoperative Period/ or exp Perioperative Nursing/
2.	((intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 during adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
4.	or/1-3
5.	limit 4 to English language
6.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
7.	5 not 6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.

16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	Fluid Therapy/
28.	((fluid* or volum*) adj3 (restor* or resuscita* or replac* or deplet* or deficien*)).ti,ab.
29.	(fluid* adj3 (challenge or bolus)).ti,ab.
30.	Colloids/
31.	exp Plasma Substitutes/
32.	albumins/ or serum albumin/
33.	Dextrans/
34.	Hydroxyethyl Starch Derivatives/
35.	exp hypertonic solutions/ or exp isotonic solutions/
36.	Gelatin/
37.	(crystalloid* or colloid* or isotonic).ti,ab.
38.	(albumin* or albumex or Albunorm or Octalbin or Zenalb or Flexbumin).ti,ab.
39.	(dextran or RescueFlow).ti,ab.
40.	(Gelatin or gelospan or Gelofusine or Geloplasma or Isoplex or Volplex).ti,ab.
41.	(starch* or hetastarch* or Pentastarch* or pentaspan* or haemaccel or HAES-steril or Hemohes or Tetrastarch* or Tetraspan or Venofundin or Volulyte or Voluven).ti,ab.
42.	(hypertonic or HyperHAES or hypotonic).ti,ab.
43.	potassium chloride/ or sodium chloride/
44.	Sodium Bicarbonate/
45.	(sodium or salin* or hartman* or ringer* or glucose or lactate* or acetate*).ti,ab.
46.	(dextrose or potassium or bicarbonate).ti,ab.
47.	(goal adj1 (direct* or orient*) adj1 therap*).ti,ab.
48.	(plasmalyte or plasma-lyte).ti,ab.
49.	or/27-48
50.	randomized controlled trial.pt.
51.	controlled clinical trial.pt.
52.	randomi#ed.ab.
53.	placebo.ab.
54.	randomly.ab.
55.	clinical trials as topic.sh.
56.	trial.ti.
57.	or/50-56
58.	Meta-Analysis/
59.	Meta-Analysis as Topic/

60.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
61.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
62.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
63.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
64.	(search* adj4 literature).ab.
65.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
66.	cochrane.jw.
67.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
68.	or/58-67
69.	26 and 49 and (57 or 68)

Embase (Ovid) search terms

1.	*peroperative care/ or *intraoperative period/ or *perioperative nursing/ or *surgical patient/
2.	((intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 during adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
4.	or/1-3
5.	limit 4 to English language
6.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
7.	5 not 6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	fluid therapy/
26.	((fluid* or volum*) adj3 (restor* or resuscita* or replac* or deplet* or deficien*)).ti,ab.
27.	(fluid* adj3 (challenge or bolus)).ti,ab.
28.	Hartmann solution/
29.	Ringer lactate solution/ or Ringer solution/

30.	acetic acid plus gluconate sodium plus magnesium chloride plus potassium chloride plus sodium chloride/
31.	polygeline/
32.	crystalloid/
33.	gelatin succinate/
34.	human serum albumin/
35.	human albumin/
36.	colloid/
37.	exp plasma substitute/
38.	albuminoid/ or serum albumin/
39.	dextran/
40.	hetastarch derivative/
41.	hypertonic solution/ or isotonic solution/
42.	gelatin/
43.	potassium chloride/ or sodium chloride/
44.	bicarbonate/
45.	(crystalloid* or colloid* or isotonic).ti,ab.
46.	(albumin* or albumex or Albunorm or Octalbin or Zenalb or Flexbumin).ti,ab.
47.	(dextran or RescueFlow).ti,ab.
48.	(Gelatin or gelospan or Gelofusine or Geloplasma or Isoplex or Volplex).ti,ab.
49.	(starch* or hetastarch* or Pentastarch* or pentaspan* or haemaccel or HAES-steril or Hemohes or Tetrastarch* or Tetraspan or Venofundin or Volulyte or Voluven).ti,ab.
50.	(hypertonic or HyperHAES or hypotonic).ti,ab.
51.	(sodium or salin* or hartman* or ringer* or glucose or lactate* or acetate*).ti,ab.
52.	(dextrose or potassium or bicarbonate).ti,ab.
53.	(goal adj1 (direct* or orient*) adj1 therap*).ti,ab.
54.	(plasmalyte or plasma-lyte).ti,ab.
55.	((plasma or blood) adj (substitute* or expand*)).ti,ab.
56.	or/25-55
57.	random*.ti,ab.
58.	factorial*.ti,ab.
59.	(crossover* or cross over*).ti,ab.
60.	((doubl* or singl*) adj blind*).ti,ab.
61.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
62.	crossover procedure/
63.	single blind procedure/
64.	randomized controlled trial/
65.	double blind procedure/
66.	or/57-65
67.	systematic review/
68.	Meta-Analysis/
69.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
70.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
71.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
72.	(search strategy or search criteria or systematic search or study selection or data

	extraction).ab.
73.	(search* adj4 literature).ab.
74.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
75.	cochrane.jw.
76.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
77.	or/67-76
78.	24 and 56
79.	78 and (66 or 77)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Intraoperative Care] this term only
#2.	MeSH descriptor: [Intraoperative Period] this term only
#3.	MeSH descriptor: [Perioperative Nursing] this term only
#4.	(or #1-#3)
#5.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) near/3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)):ti,ab
#6.	((care* or caring or treat* or nurs* or recover* or monitor*) near/3 during near/3 (surg* or operat* or anaesthes* or anesthes*)):ti,ab
#7.	(or #4-#6)
#8.	MeSH descriptor: [Fluid Therapy] explode all trees
#9.	((fluid* or volum*) near/3 (restor* or resuscita* or replac* or deplet* or deficien*)):ti,ab
#10.	(fluid* near/3 (challenge or bolus)):ti,ab
#11.	MeSH descriptor: [Colloids] explode all trees
#12.	MeSH descriptor: [Plasma Substitutes] explode all trees
#13.	MeSH descriptor: [Albumins] explode all trees
#14.	MeSH descriptor: [Serum Albumin] explode all trees
#15.	MeSH descriptor: [Dextrans] explode all trees
#16.	MeSH descriptor: [Hydroxyethyl Starch Derivatives] explode all trees
#17.	MeSH descriptor: [Hypertonic Solutions] explode all trees
#18.	MeSH descriptor: [Gelatin] explode all trees
#19.	(crystalloid* or colloid* or isotonic):ti,ab
#20.	(albumin* or albumex or Albunorm or Octalbin or Zenalb or Flexbumin):ti,ab
#21.	(dextran or RescueFlow):ti,ab
#22.	(Gelatin or gelospan or Gelofusine or Geloplasma or Isoplex or Volplex):ti,ab
#23.	(starch* or hetastarch* or Pentastarch* or pentaspan* or haemaccel or HAES-steril or Hemohes or Tetrastarch* or Tetraspan or Venofundin or Volulyte or Voluven):ti,ab
#24.	(hypertonic or HyperHAES or hypotonic):ti,ab
#25.	MeSH descriptor: [Potassium Chloride] explode all trees
#26.	MeSH descriptor: [Sodium Chloride] explode all trees
#27.	MeSH descriptor: [Sodium Bicarbonate] explode all trees
#28.	(sodium or salin* or hartman* or ringer* or glucose or lactate* or acetate*):ti,ab
#29.	(dextrose or potassium or bicarbonate):ti,ab
#30.	(goal near/1 (direct* or orient*) near/1 therap*):ti,ab
#31.	(plasmalyte or plasma-lyte):ti,ab
#32.	((plasma or blood) near/1 (substitute* or expand*)):ti,ab

#33.	(or #8-#32)
#34.	#7 and #33

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the perioperative care population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run on Medline and Embase.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 30 May 2019	Exclusions Health economics studies
Embase	2014 – 30 May 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 02 May 2019 NHSEED - Inception to 02 May 2019	None

Medline (Ovid) search terms

1.	exp Preoperative Care/ or exp Perioperative Care/ or exp Perioperative Period/ or exp Perioperative Nursing/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
5.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
6.	1 or 2 or 3 or 4 or 5
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.
8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	7 or 8
10.	postoperative care/ or exp Postoperative Period/ or exp Perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.
12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.
14.	10 or 11 or 12 or 13
15.	exp Preoperative Care/ or Preoperative Period/
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.

17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	6 or 9 or 14 or 18
20.	letter/
21.	editorial/
22.	news/
23.	exp historical article/
24.	Anecdotes as Topic/
25.	comment/
26.	case report/
27.	(letter or comment*).ti.
28.	or/20-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animals/ not humans/
32.	exp Animals, Laboratory/
33.	exp Animal Experimentation/
34.	exp Models, Animal/
35.	exp Rodentia/
36.	(rat or rats or mouse or mice).ti.
37.	or/30-36
38.	19 not 37
39.	limit 38 to English language
40.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
41.	39 not 40
42.	economics/
43.	value of life/
44.	exp "costs and cost analysis"/
45.	exp Economics, Hospital/
46.	exp Economics, medical/
47.	Economics, nursing/
48.	economics, pharmaceutical/
49.	exp "Fees and Charges"/
50.	exp budgets/
51.	budget.ti,ab.
52.	cost*.ti.
53.	(economic* or pharmaco?economic*).ti.
54.	(price* or pricing*).ti,ab.
55.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
56.	(financ* or fee or fees).ti,ab.
57.	(value adj2 (money or monetary)).ti,ab.
58.	or/42-57
59.	41 and 58

Embase (Ovid) search terms

1.	*preoperative period/ or *intraoperative period/ or *postoperative period/ or *perioperative nursing/ or *surgical patient/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
5.	1 or 2 or 3 or 4
6.	peroperative care/ or exp peroperative care/ or exp perioperative nursing/
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.
8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	6 or 7 or 8
10.	postoperative care/ or exp postoperative period/ or perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.
12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.
14.	10 or 11 or 12 or 13
15.	exp preoperative care/ or preoperative period/
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	5 or 9 or 14 or 18
20.	letter.pt. or letter/
21.	note.pt.
22.	editorial.pt.
23.	case report/ or case study/
24.	(letter or comment*).ti.
25.	or/20-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animal/ not human/
29.	nonhuman/
30.	exp Animal Experiment/
31.	exp Experimental Animal/
32.	animal model/
33.	exp Rodent/
34.	(rat or rats or mouse or mice).ti.
35.	or/27-34
36.	19 not 35

37.	limit 36 to English language
38.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
39.	37 not 38
40.	health economics/
41.	exp economic evaluation/
42.	exp health care cost/
43.	exp fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	39 and 53

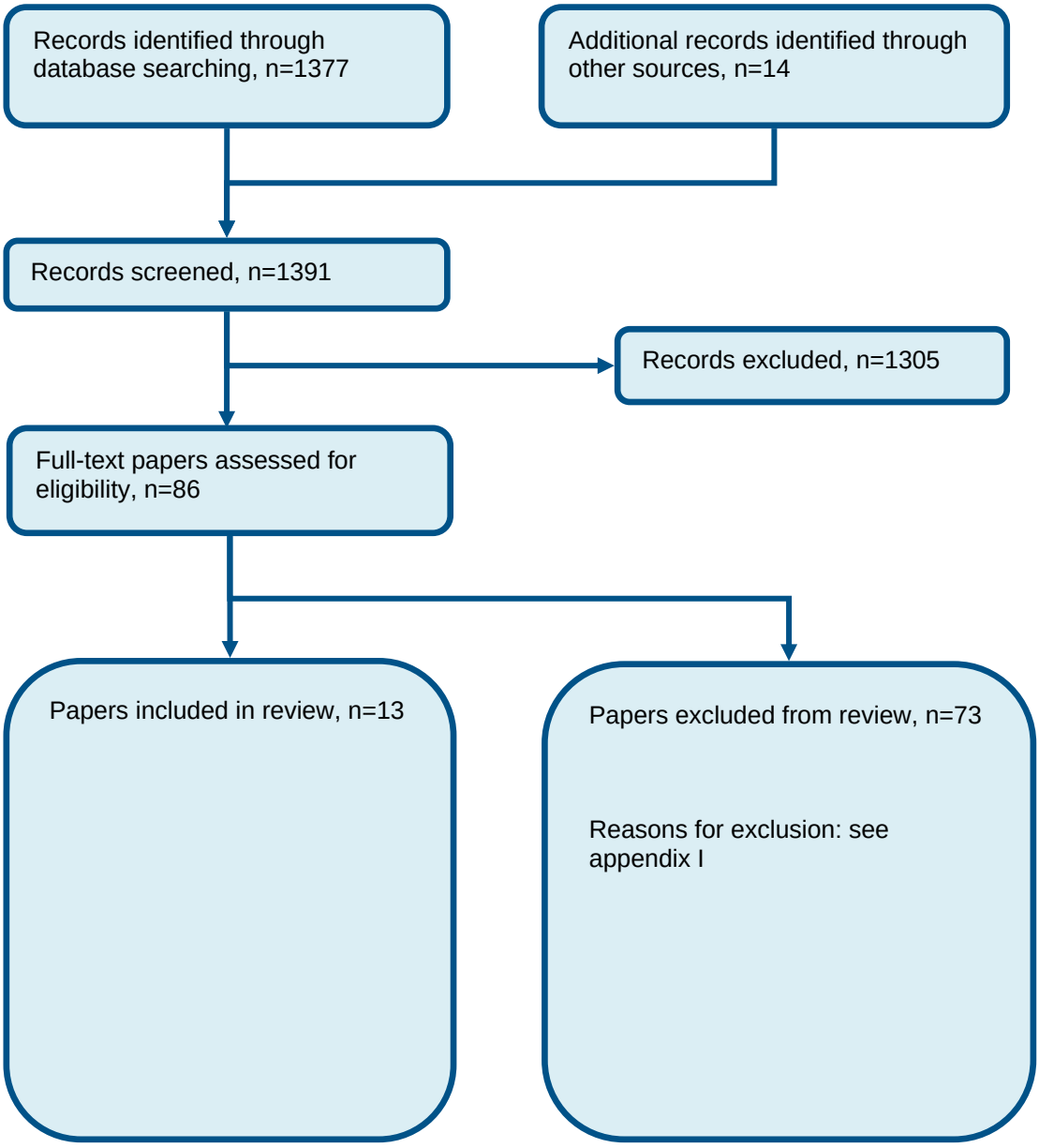
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Preoperative Care EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Perioperative Care EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Perioperative Period EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Perioperative Nursing EXPLODE ALL TREES
#5.	(((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#6.	(((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#7.	(((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#8.	(((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10.	(* IN HTA)
#11.	(* IN NHSEED)
#12.	#9 AND #10
#13.	#9 AND #11
#14.	MeSH DESCRIPTOR Intraoperative Care EXPLODE ALL TREES
#15.	#1 OR #2 OR #3 OR #4 OR #14
#16.	((intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*))
#17.	(((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#18.	((postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*))
#19.	((after adj3 (surg* or operat* or anaesthes* or anesthes*)))

#20.	((post adj3 (operat* or anaesthes* or anesthes*)))
#21.	((pre-operat* or preoperat* or pre-surg* or presurg*))
#22.	(((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#23.	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24.	#10 AND #23
#25.	#11 AND #23
#26.	#12 OR #13 OR #24 OR #25

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of intravenous fluid management strategy.



Appendix D: Clinical evidence tables

Study	Abdallah 2014[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=44)
Countries and setting	Conducted in Egypt; Setting: Nephrology Department Medical Sugar Center and Theodor Bilharz Research Institute, Cairo, Egypt
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 days post op
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Inclusion criteria	Patients with end-stage renal disease and scheduled for living donor renal transplantation between September 2012 and January attending the Nephrology Department Medical Sugar Center and Theodor Bilharz Research Institute, Cairo, Egypt
Exclusion criteria	Patients with cardiac disease and liver dysfunction were excluded from the study
Recruitment/selection of patients	patients scheduled for a living donar renal transplanation at the Nephrology Department Medical Sugar Center and Theodor Bilharz Research Institute, Cairo, Egypt
Age, gender and ethnicity	Age - Mean (SD): 54.35 +-11.5 years. Gender (M:F): 32/12. Ethnicity: n/a
Further population details	1. Age: <60 years (20-58). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (not stated). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear (not stated).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Colloid - Albumin. Intravenous infusion of 20 % human albumin with 0.9 % normal saline was given intravenously over 1 h before unclamping of vascular anastomosis . Duration 218.5 - (37.56) mins. Concurrent medication/care: Preoperative hemodialysis 24 h before renal transplant surgery was performed for 36 patients Oral cyclosporine and mycophenolate mofetil were given to patients 24 h before surgery, and methylprednisolone (500 mg) was given at induction of anesthesia. General anesthesia was induced. A central venous catheter was inserted after induction of anesthesia in the right internal jugular vein. Intravenous fluids were given to maintain CVP at 10–15 mm Hg until the end of

	surgery. Furosemide (30 mg i.v.) was given when indicated in the albumin and saline groups after vascular anastomosis to improve diuresis. At the end of surgery, the studied fluid was discontinued and all patients received an infusion of normal saline 0.9 % and glucose 5 % at the rate of 40 ml/h. Hourly urine output was replaced with 1 ml 0.9 % normal saline for each ml of urine.. Indirectness: No indirectness (n=22) Intervention 2: Crystalloid - Sodium chloride 0.9% (normal saline). intraoperative intravenous infusion of 0.9 % normal saline alone. Duration 228.1 +- (38.58). Concurrent medication/care: Preoperative hemodialysis 24 h before renal transplant surgery was performed for 36 patients Oral cyclosporine and mycophenolate mofetil were given to patients 24 h before surgery, and methylprednisolone (500 mg) was given at induction of anesthesia.General anesthesia was induced. A central venous catheter was inserted after induction of anesthesia in the right internal jugular vein. Intravenous fluids were given to maintain CVP at 10–15 mm Hg until the end of surgery.Furosemide (30 mg i.v.) was given when indicated in the albumin and saline groups after vascular anastomosis to improve diuresis. At the end of surgery, the studied fluid was discontinued and all patients received an infusion of normal saline 0.9 % and glucose 5 % at the rate of 40 ml/h. Hourly urine output was replaced with 1 ml 0.9 % normal saline for each ml of urine. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALBUMIN versus SODIUM CHLORIDE 0.9% (NORMAL SALINE) Protocol outcome 1: Adverse events and complications - Actual outcome: pulmonary edema at unclear; Group 1: 1/22, Group 2: 2/22; Comments: Three patients had evidence of pulmonary edema on chest X-ray [one (4.5 %) in the albumin group and two (9.1 %) in the saline group and were treated conservatively with Furosemide. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: The most common causes of end-stage renal disease in both groups were diabetes mellitus, hypertension, and glomerulone-phritis. 32 males (72.7 %) and 12 females (27.3 %) with a mean age of 54.35 ± 11.15 years (range 20–58 years); Blinding details: no details given; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit

Study	Farag 2012[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in USA; Setting:
Line of therapy	Unclear
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall:
Subgroup analysis within study	Not applicable:
Inclusion criteria	patients scheduled for complex spine surgery (single segment with instrumentation or multiple-segment laminectomies with or without instrumentation) in prone position
Exclusion criteria	not stated
Recruitment/selection of patients	factorially randomized into four groups: 5% albumin and topical placebo; 5% albumin and topical brimonidine; lactated Ring-er's solution and topical placebo; and lactated Ringer's solution and topical brimonidine
Age, gender and ethnicity	Age - Mean (SD): 60 (+-8) 57 (+-15). Gender (M:F): 27/33. Ethnicity:
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Colloid - Albumin. 5% human albumin and either topical placebo or topical brimonidine. Duration 5.7 +-2.2. Concurrent medication/care: All the patients were given 5–7 ml/kg lactated Ringer's solution in the immediate preoperative period, which was followed by 6–7 ml/kg/h lactated Ringer's solution for maintenance. . Indirectness: No indirectness (n=29) Intervention 2: Crystalloid - Lactated Ringer's (USP). lactated Ringer's solution and topical placebo or topical brimonidine. Duration 5.7 +- 1.9. Concurrent medication/care: All the patients were given 5–7 ml/kg lactated Ringer's solution in the immediate preoperative period, which was followed by 6–7 ml/kg/h lactated Ringer's solution for maintenance.. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALBUMIN versus LACTATED RINGER'S (USP)

Protocol outcome 1: Length of hospital stay
- Actual outcome: duration of hospitalisation at not specified ;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Length of stay in intensive care unit
- Actual outcome: length of ICU stay at not specified ;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Mortality ; Adverse events and complications ; Unplanned ICU admission

Study	Feldheiser 2013[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Germany; Setting: University Hospital Charite, Campus Virchow-Clinic in Berlin
Line of therapy	Unclear
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were stratified by the presence or absence of preoperative ascites. Eligible patients were adults undergoing laparotomy to perform cytoreductive surgery due to primary ovarian cancer at the University Hospital Charite´ , Campus Virchow-Clinic in Berlin
Exclusion criteria	no details provided
Age, gender and ethnicity	no details (supplementary table)
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation:
Extra comments	no details (supplementary table) .
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Crystalloid - Plasma. Balanced Crystalloid. Duration 4 hours . Concurrent medication/care: study fluids was started intraoperatively after induction of anaesthesia and establishing haemodynamic monitoring via arterial and central venous lines and oesophageal Doppler (CardioQ TM, Deltex Medical, Chichester, UK), and finished at the end of surgery. Haemodynamic measurements were performed before and after each administration of study fluid, after every haemodynamic change of mean arterial pressure or heart rate or at least every 15 min. . Indirectness: No indirectness (n=26) Intervention 2: Colloid - Starches. Balanced Starch (HED, 130/0.4, 6%). Duration 4 hours. Concurrent medication/care: Haemodynamic measurements were performed before and after each administration of study fluid, after every haemodynamic change of mean arterial pressure or heart rate or at least every 15

	min. . Indirectness: No indirectness
Funding	Other (funded by Fresenius Kabi - global healthcare and drug company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PLASMA versus STARCHES

Protocol outcome 1: Quality of life/health status
- Actual outcome: Health status EQ-5D of the EuroQol group - part 1 score at 3 months; group 1 part 1 median (25%-75%): 2.5 (0.3-4); group 2: 2 (2-3.8) Part 2 median (25%-75%):60 (42-80); group 2: 50 (46-74)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Comments: Unclear which components of EQ-5D are being reported

Protocol outcome 2: Mortality
- Actual outcome: mortality at 3 months; Group 1: 0/24, Group 2: 5/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: in supplementary table; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: severe breach of protocol

Protocol outcome 3: Adverse events and complications
- Actual outcome: complications: clavien-dindo grade 0 at 3 months; Group 1: 5/24, Group 2: 3/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: in supplementary table; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: severe breach of protocol
- Actual outcome: complications: clavien-dindo grade 1 at 3 months; Group 1: 0/24, Group 2: 6/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: in supplementary table; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: severe breach of protocol
- Actual outcome: complications: clavien-dindo grade 2 at 3 months; Group 1: 15/24, Group 2: 9/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: in supplementary table; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: severe breach of protocol
- Actual outcome: complications: clavien-dindo grade 3a at 3 months; Group 1: 1/24, Group 2: 1/24
Risk of bias: All domain - ; Indirectness of outcome: No indirectness
- Actual outcome: complications: clavien-dindo grade 3b at 3 months; Group 1: 3/24, Group 2: 5/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: in supplementary table; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: severe breach of protocol

Protocol outcome 4: Length of stay in intensive care unit - Actual outcome: length of stay in ITU at 3 months; Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of hospital stay ; Unplanned ICU admission

Study	Joosten 2018[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=160)
Countries and setting	Conducted in Belgium; Setting: Te study was conducted in two centers in Brussels (Brugmann and Erasme Hospitals)
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall:
Subgroup analysis within study	Not applicable:
Inclusion criteria	Inclusion criteria were adult patients scheduled to undergo general anesthesia for elective open abdominal surgery expected to last at least 3 h.
Exclusion criteria	less than 18 yr old, an American Society of Anesthesiologists physical status score greater than 3, a preoperative left ventricular ejection fraction less than 30%, significant cardiac arrhythmias or aortic regurgitation, coagulation dis- orders (activated partial thromboplastin time greater than 1.5 times normal value), preoperative renal insufficiency (serum creatinine greater than 2 mg/dl, oliguria, anuria, or hemodialysis), impaired hepatic function (phosphatase alkaline, aspartate aminotransferase, alanine aminotransferase greater than 2 times normal value), emergency surgery, preoperative infection, current pregnancy or lactation period, known allergy to HES, and participation in another trial. Additionally, patients who were found to have metastatic dissemination upon first surgical look and had their procedures cancelled (surgical time less than 3 h) were excluded. Finally, any patient that required an unexpected supra renal aortic clamping during their aortic surgery was also excluded.
Age, gender and ethnicity	Age - Median (range): 48-73. Gender (M:F): 96/64.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Crystalloid - Plasmalyte. balanced crystalloid solution (plasmalyte, Baxter, Belgium). Duration length of surgery . Concurrent medication/care: After anesthesia induction, a baseline isotonic balanced crystalloid infusion (Plasmalyte) was set at 3 ml · kg–1 · h–1 via an infusion pump (Volumat Agilia, Fresenius Kabi, Belgium) and administered for the duration of the procedure. Additional fluid boluses were delivered by a goal-directed fluid therapy strategy that used the closed-loop system and consisted of multiple

	100-ml mini-fluid challenges of the study fluid (Plasmalyte or Volulyte). In both groups, an upper limit daily dose of 33 ml/kg of the study fluid was allowed. If the upper limit of the study fluid was reached, unblinded Plasmalyte was consistently used thereafter in all patients. Importantly, the closed-loop system delivers only 100-ml fluid boluses over 6 min and is therefore not designed for bleeding resuscitation but rather fluid optimization in line with goal-directed fluid therapy protocols. As a result, the anesthesiologist in charge of the patient also had the opportunity to administer additional Plasmalyte without using the closed-loop (as rescue) in case of hemodynamic instability related to acute bleeding or aortic unclamping. No other fluids were allowed in addition to the rescue crystalloid (Plasmalyte). Lastly, if the senior anesthetist felt that the patient was fluid optimized but MAP was less than 65 mmHg (despite appropriate anesthetic depth), vasopressors could be used.. Indirectness: No indirectness (n=80) Intervention 2: Colloid - Starches. balanced colloid solution (Volulyte; Fresenius Kabi mbH,Germany). Duration duration of surgery. Concurrent medication/care: After anesthesia induction, a baseline isotonic balanced crystalloid infusion (Plasmalyte) was set at 3 ml · kg–1 · h–1 via an infusion pump (Volumat Agilia, Fresenius Kabi, Bel gium) and administered for the duration of the procedure. Additional fluid boluses were delivered by a goal-directed fluid therapy strategy that used the closed-loop system and consisted of multiple 100-ml mini-fluid challenges of the study fluid (Plasmalyte or Volulyte). In both groups, an upper limit daily dose of 33 ml/kg of the study fluid was allowed. If the upper limit of the study fluid was reached, unblinded Plasmalyte was consistently used thereafter in all patients. Importantly, the closed-loop system delivers only 100-ml fluid boluses over 6 min and is therefore not designed for bleeding resuscitation but rather fluid optimization in line with goal-directed fluid therapy protocols. As a result, the anesthesiologist in charge of the patient also had the opportunity to administer additional Plasmalyte without using the closed-loop (as rescue) in case of hemodynamic instability related to acute bleeding or aortic unclamping. No other fluids were allowed in addition to the rescue crystalloid (Plasmalyte). Lastly, if the senior anesthetist felt that the patient was fluid optimized but MAP was less than 65 mmHg (despite appropriate anesthetic depth), vasopressors could be used.. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PLASMALYTE versus STARCHES

Protocol outcome 1: Mortality
- Actual outcome: mortality at 30 days post op; Group 1: 4/80, Group 2: 0/80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: duration of surgery in crystalloid group lasted 1 hour longer

Protocol outcome 2: Adverse events and complications
- Actual outcome: patients with major complications at 30 days post op; Group 1: 23/80, Group 2: 9/80

	Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: duration of surgery in crystalloid group lasted 1 hour longer - Actual outcome: acute kidney injury at 30 days post op; Group 1: 23/80, Group 2: 19/80 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: duration of surgery in crystalloid group lasted 1 hour longer - Actual outcome: nausea and vomiting at 30 days post op; Group 1: 33/80, Group 2: 28/80 Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: duration of surgery in crystalloid group lasted 1 hour longer - Actual outcome: pulmonary complications (embolism, edema, pneumonia) at 30 days post op; Group 1: 14/80, Group 2: 4/80 Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: duration of surgery in crystalloid group lasted 1 hour longer - Actual outcome: superficial wound infection at 30 days post op; Group 1: 6/80, Group 2: 5/80 Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: duration of surgery in crystalloid group lasted 1 hour longer
Protocol outcomes not reported by the study	Quality of life ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit

Study	Moretti 2003[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	People undergoing major elective general, gynecological, orthopedic, or urologic surgery with an anticipated blood loss of >500 mL
Exclusion criteria	Patients with the following conditions were excluded from the study: coagulopathy, significant hepatic (liver enzymes >50% upper limit of normal values) or renal (creatinine >50% upper limit of normal values) dysfunction, and congestive heart failure. Those who had received an investigational drug within the last 30 days and those with known hypersensitivity to hydroxyethyl starches were also excluded.
Age, gender and ethnicity	Age - Mean (SD): Crystalloid gorup: 58.8, Colloid groups: 58.11 and 59.8 . Gender (M:F): Not stated. Ethnicity:
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: Systematic review: mixed (ASA I-III). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Systematic review: mixed
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Crystalloid - Lactated Ringer's (USP). Patients received lactated Ringer's solution for the treatment of hypovolemia according to a hypovolemia algorithm. . Duration As needed until discharge/death. . Concurrent medication/care: Before the induction of anaesthesia, all patients received an IV bolus of 7 mL/kg of lactated Ringer's solution (crystalloid) was administered followed by an IV infusion of lactated Ringer's solution at a rate of 5 mL/kg1 /h1 throughout surgery. . Indirectness: No indirectness (n=60) Intervention 2: Colloid - Starches. Patients received either 6% hetastarch in saline or Hextendt for the

	treatment of hypovolemia according to a hypovolemia algorithm. N=60. Duration As needed until discharge/death. . Concurrent medication/care: Before the induction of anaesthesia, all patients received an IV bolus of 7 mL/kg of lactated Ringer's solution (crystalloid) was administered followed by an IV infusion of lactated Ringer's solution at a rate of 5 mL/kg1 /h1 throughout surgery.. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Supported in part by a grant from BioTime, Inc., Berkeley, CA.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTATED RINGER'S (USP) versus STARCHES Protocol outcome 1: Adverse events and complications - Actual outcome: Nausea at post-operative data ; Group 1: 22/30, Group 2: 25/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit

Study	Shah 2014[70]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in India; Setting: not specified
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7 days post op
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall:
Subgroup analysis within study	Not applicable
Inclusion criteria	18 and 65 years, having an American Society of Anesthesiologist Physical Scoring (ASA PS) risk between III or IV, scheduled for living donor renal transplantation between March 2012 and June 2012.
Exclusion criteria	The exclusion criteria were age <18 years, severe cardiovascular disease, liver dysfunction, and diabetes mellitus
Age, gender and ethnicity	Age - Mean (SD): albumin 35.1 (+- 10.43) saline 31.7 (+-10.05). Gender (M:F): 33/7.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Colloid - Albumin. 0.9% normal saline with 20% human albumin. Duration 229.7 (±49.45). Concurrent medication/care: Intravenous fluids were given to maintain central venous pressure (CVP) at 12–15 mm Hg till the end of the vascular anastomosis and 10–12 mm Hg after anastomosis till the end of surgery. Twenty percent of mannitol 0.5 mg/kg IV was given before declamping the renal vessels in both the groups. At the end of surgery, the study fluid was discontinued and all the patients received an infusion of dextrose 5%/0.45% normal saline at rate of 50 mL/hour. The hourly urine output was replaced with 0.45% of normal saline 1 mL for each milliliter of urine.. Indirectness: No indirectness (n=40) Intervention 2: Crystalloid - Sodium chloride 0.9% (normal saline). 0.9% normal saline. Duration 209.2 (±48.89). Concurrent medication/care: At the end of surgery, the study fluid was discontinued and all the patients received an infusion of dextrose 5%/0.45% normal saline at rate of 50 mL/hour. The hourly urine output was replaced with 0.45% of normal saline 1 mL for each milliliter of urine.. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALBUMIN versus SODIUM CHLORIDE 0.9% (NORMAL SALINE) Protocol outcome 1: Adverse events and complications - Actual outcome: pulmonary edema at up to 7 days; Group 1: 1/40, Group 2: 2/40 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit

Study	Szturz 2014[74]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=115)
Countries and setting	Conducted in Czech Republic; Setting: operating theatres of an intensive care unit (ICU) of a tertiary hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	115 consecutive patients undergoing elective major urological surgery
Exclusion criteria	under 21 years, emergency surgery, pregnancy, severe cardiac or respiratory failure and expected duration of surgery less than 90 minutes
Age, gender and ethnicity	Age - Median (range): 22-93. Gender (M:F): 83/32.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation:
Extra comments	patients over 21 years undergoing elective major urological surgery
Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Colloid - Starches. hydroxyethyl starch (HES, Voluven, Fresenius Kabi AG, Bad Homburg, Germany). Duration length of surgery - over 90 mins. Concurrent medication/care: After the induction, each patient obtained a TED probe (HemosonicTM 100 hemodynamic optimization (fl uid therapy with Ringer's solution or hydroxyethyl starch 6 % 130/0.4 and administration of vasoactive drugs) was started according to TED variables to maintain the cardiac index (CI) between 2.6 and 3.8 l/min/m2. In each patient from any of the groups, the probe was inserted through the mouth to the distal third of the esophagus. According to the predefined therapeutic management algorithm (Fig. 2), fluids, inotropic support with dobutamine (Dobutamin Lachema 250, Pliva-Lachema a.s., Brno, Czech Republic), and vasoactive support with noradrenaline (Noradrenalin Leciva, Zentiva, Czech Republic) or isosorbide dinitrate (Isoketoztok 0.1 %, Schwarz Pharma AG, Monheim, Germany) were used. All patients had their bowels prepared by enema and/or using phosphate solution in the evening before surgery. This therapy was extended by administration of bisacodyl (Fenolax, ICN Polfa, Rzeszow, Poland) and colonoscopy preparation diet in case of planned radical cystectomy. The patients were encouraged to drink water until midnight. Intravenous fl uids, usually used overnight to minimize dehydration before surgery, were not administered due to local urological recommendations. General anesthesia was induced with propofol and

	maintained with a balanced technique incorporating mixed nitrous oxide and oxygen, isofl urane with cisatracurium providing muscle relaxation. Sufentanil was used for analgesia at the anesthetist's discretion. The patients were intubated and ventilated to normocapnia throughout the operation. Standard monitoring included ECG, pulse oxymetry, capnography, and measurement of invasive arterial blood pressure. Prior to the operation, central venous catheter was introduced in 50 patients (88 %) in the CRY group and 49 patients (84 %) in the COL group. Intraoperative epidural analgesia was never used.. Indirectness: No indirectness (n=57) Intervention 2: Crystalloid - Ringer's acetate. Ringer's solution (Ringer's injection, Fresenius Kabi, Verona, Italy). Duration length of surgery - over 90 mins. Concurrent medication/care: After the induction, each patient obtained a TED probe (HemosonicTM 100 hemodynamic optimization (fl uid therapy with Ringer's solution or hydroxyethyl starch 6 % 130/0.4 and administration of vasoactive drugs) was started according to TED variables to maintain the cardiac index (CI) between 2.6 and 3.8 l/min/m2. In each patient from any of the groups, the probe was inserted through the mouth to the distal third of the esophagus. According to the predefined therapeutic management algorithm (Fig. 2), fluids, inotropic support with dobutamine (Dobutamin Lachema 250, Pliva-Lachema a.s., Brno, Czech Republic), and vasoactive support with noradrenaline (Noradrenalin Leciva, Zentiva, Czech Republic) or isosorbide dinitrate (Isoketoztok 0.1 %, Schwarz Pharma AG, Monheim, Germany) were used. All patients had their bowels prepared by enema and/or using phosphate solution in the evening before surgery. This therapy was extended by administration of bisacodyl (Fenolax, ICN Polfa, Rzeszow, Poland) and colonoscopy preparation diet in case of planned radical cystectomy. The patients were encouraged to drink water until midnight. Intravenous fl uids, usually used overnight to minimize dehydration before surgery, were not administered due to local urological recommendations. General anesthesia was induced with propofol and maintained with a balanced technique incorporating mixed nitrous oxide and oxygen, isofl urane with cisatracurium providing muscle relaxation. Sufentanil was used for analgesia at the anesthetist's discretion. The patients were intubated and ventilated to normocapnia throughout the operation. Standard monitoring included ECG, pulse oxymetry, capnography, and measurement of invasive arterial blood pressure. Prior to the operation, central venous catheter was introduced in 50 patients (88 %) in the CRY group and 49 patients (84 %) in the COL group. Intraoperative epidural analgesia was never used.. Indirectness: No indirectness
Funding	Funding not stated ( )

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STARCHES versus RINGER'S ACETATE

Protocol outcome 1: Adverse events and complications
- Actual outcome: gastrointestinal tract dysfunction at 28 days; Group 1: 18/58, Group 2: 9/57
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: The research nurse assigning the patients to either the crystalloid (CRY, n = 57) or colloid (COL, n = 58) groups opened the allocation envelope immediately before induction of general anesthesia; Group 1 Number missing: 0;

Group 2 Number missing: 0 Protocol outcome 2: Length of hospital stay - Actual outcome: Length of hospital stay at not stated; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: The research nurse assigning the patients to either the crystalloid (CRY, n = 57) or colloid (COL, n = 58) groups opened the allocation envelope immediately before induction of general anesthesia; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of stay in intensive care unit - Actual outcome: ICU length of stay at not stated; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: The research nurse assigning the patients to either the crystalloid (CRY, n = 57) or colloid (COL, n = 58) groups opened the allocation envelope immediately before induction of general anesthesia; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Unplanned ICU admission

Study	Werner 2018[84]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=63)
Countries and setting	Conducted in Germany; Setting: University Hospital Charité, Campus Virchow-Klinikum Berlin, Germany; the Vivantes Humboldt Klinikum Berlin, Germany; and the University Hospital Bonn, Germany
Line of therapy	Unclear
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall:
Subgroup analysis within study	Not applicable:
Inclusion criteria	aged 18 years or older and aged 80 years or younger, scheduled for elective surgery of the pancreatic head due to primary pancreatic cancer or chronic pancreatitis
Exclusion criteria	chronic heart failure defined as greater than class II according to the New York Heart Association (NYHA), American Society of Anesthesiologists (ASA) classification status greater thanIII, renal insufficiency (serumcreatinine>1,5mgdL1 or >130mmol L□1) or dependency on hemodialysis, impaired hepatic function(Quick-value<60%or liver cirrhosis Child–Pugh C), history of bleeding disorder or known bleeding diathesis, hematocrit □25%, aneurysm of the ascending and/or thoracic aorta, patients with any local esophageal disease, additiona contraindications for application of study medication, pregnancy or lactation period, emergency surgery, simultaneous participation in another interventional clinical trial, and detained patients by judicial or enforceable order.
Recruitment/selection of patients	adults, aged 18 years or older and aged 80 years or younger, scheduled for elective surgery of the pancreatic head due to primary pancreatic cancer or chronic pancreatitis
Age, gender and ethnicity	Age - Mean (range): 50-72. Gender (M:F): not given .
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation:
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Colloid - Starches. hyperoncotic balanced 10% HES 130/0.42 solution (Tetraspan 10%, B. Braun, Melsungen, Germany). Duration 330 mins median. Concurrent medication/care: The hemodynamic management was performed according to a goal-directed hemodynamic algorithm guided by the esophageal Doppler monitor (EDM, CardioQ-ODMTM, Deltex Medical, Chichester, UK),[10,11] while the volume of study fluid for the fluid challenges was 250 mL (Supplemental Digital Content—Figure S1, http://

	links.lww.com/MD/C224). Briefly, after induction of anesthesia and establishing the hemodynamic monitoring an initial fluid challenge of 250 mL of intravenous study fluid was given over 5 minutes. If the EDM detected an increase of stroke volume (SVEDM) <10% no further fluid challenge was performed. If SVEDM increased ≥10%, additional fluid challenges with an intravenous bolus of 250 mL study fluid were given until no further increase of SVEDM ≥10% could be measured. After a period of 15 minutes or acute hemodynamic deterioration SVEDM was measured again and a decrease of >10% compared with SVEDM after the last fluid challenge re-indicated further fluid challenges. The maximum doses for 10% and 6%HES solutions were 30 and 50 mL kg□1 body weight (BW), respectively, corresponding to a maximum dose of 3gkg□1 BW per day. After reaching the maximum dose, in the 10% HES group, the blinded treatment was continued with balanced crystalloid solution up to a dose of 50 mL kg□1 BW. Then an open-label balanced crystalloid solution was used for further fluid challenges within the goal- directed hemodynamic algorithm until the end of surgery. Regarding the 6% HES and crystalloid solution, similarly, at the maximum dose of 50 mL kg□1 BW, open-label balanced crystalloid solution was used if further fluid challenges were required within the goal-directed hemodynamic algorithm.. Indirectness: No indirectness (n=22) Intervention 2: Colloid - Starches. isooncotic balanced 6% HES 130/0.42 solution (Tetraspan 6%, B. Braun). Duration 330 mins median. Concurrent medication/care: The maximum doses for 10% and 6%HES solutions were 30 and 50 mL kg□1 body weight (BW), respectively, corresponding to a maximum dose of 3gkg□1 BW per day. After reaching the maximum dose, in the 10% HES group, the blinded treatment was continued with balanced crystalloid solution up to a dose of 50 mL kg□1 BW. Then an open-label balanced crystalloid solution was used for further fluid challenges within the goal-directed hemodynamic algorithm until the end of surgery. Regarding the 6% HES and crystalloid solution, similarly, at the maximum dose of 50 mL kg□1 BW, open-label balanced crystalloid solution was used if further fluid challenges were required within the goal-directed hemodynamic algorithm.. Indirectness: No indirectness (n=21) Intervention 3: Crystalloid - Plasma. balanced crystalloid solution (Sterofundin ISO, B. Braun). Duration 335 mins median. Concurrent medication/care: The maximum doses for 10% and 6%HES solutions were 30 and 50 mL kg□1 body weight (BW), respectively, corresponding to a maximum dose of 3gkg□1 BW per day. After reaching the maximum dose, in the 10% HES group, the blinded treatment was continued with balanced crystalloid solution up to a dose of 50 mL kg□1 BW. Then an open-label balanced crystalloid solution was used for further fluid challenges within the goal directed hemodynamic algorithm until the end of surgery. Regarding the 6% HES and crystalloid solution, similarly, at the maximum dose of 50 mL kg□1 BW, open-label balanced crystalloid solution was used if further fluid challenges were required within the goal-directed hemodynamic algorithm.. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STARCHES versus PLASMA

Protocol outcome 1: Adverse events and complications

- Actual outcome: acute kidney infection at 15 days; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: lower body weight in 6% HES and shorter period of preoperative fasting in the 10% HES group	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit

Study	Yates 2014[87]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=202)
Countries and setting	Conducted in United Kingdom
Line of therapy	Unclear
Duration of study	Intervention + follow up: post-operative day 5
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Over 55 years of age undergoing elective colorectal resection. Patients must have an Oxygen Consumption at their AnaerobicThreshold of less than or equal to 14ml.kg-1min-1
Exclusion criteria	Patients less than 55 years of age. Patients having emergency procedures. Those who are ASA grade 5. Patients who refuse or are unable to give informed consent. Renal failure with oliguria or anuria not related to hypovolaemia. Patients receiving dialysis treatment. Intracranial bleeding. Known hypersensitivity to hydroxyethyl starches or gelatins. Patients with sodium overload. Patients who have had inadequate time (<24 hours) to consider thePatient Information Leaflet. Patients with Hypertrophic Obstructive Cardiomyopathy (HOCM), moderate to severe aortic stenosis, phaeochromocytoma, a low platelet count, or have used a monoamine oxidase inhibitor within the last 14 days.
Age, gender and ethnicity	Age - Median (range): Crystalloid: 70 (56-87); colloid: 72 (56-88). . Gender (M:F): Male (%): Crystalloid geroup 54, colloid group 63.
Further population details	1. Age: >60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=98) Intervention 1: Crystalloid - Hartmann's. Balanced crystalloid (Hartmann's solution) as haemodynamic optimization fluid. . Duration 5 days post-operation. Concurrent medication/care: All patients received an IV infusion of Hartmann's solution at a rate of 1.5 ml kg-1 h-1 from the start of the trial period and this continued for 24 h. . Indirectness: No indirectness (n=104) Intervention 2: Colloid - Starches. Balanced 6% hydroxyethyl starch (130/0.4, Volulyte) as hameodynamic optimisation fluid. . Duration 5 days post-operation. Concurrent medication/care: All patients

	received an IV infusion of Hartmann's solution at a rate of 1.5 ml kg-1 h-1 from the start of the trial period and this continued for 24 h. . Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Unrestricted grant from Fresenium Kabi)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HARTMANN'S versus STARCHES Protocol outcome 1: Mortality - Actual outcome: Mortality at Unclear; Group 1: 2/98, Group 2: 5/104 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events and complications - Actual outcome: People with major complications at Unclear; Group 1: 19/98, Group 2: 26/104 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Length of hospital stay - Actual outcome: Length of hospital stay at until discharge; p: 0.74, Comments: There was little difference in hospital length of stay between the groups - a median of 8 days in the crystalloid group and 9days in the HES group.); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Unplanned ICU admission ; Length of stay in intensive care unit

Study	Zhang 2012[89]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in China; Setting:
Line of therapy	Unclear
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ±
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	People who were undergoing elective gastrointestinal surgeries with an anticipated blood loss of less than 500 ml were included in the study. The inclusion criteria were patients with gastric or colonic cancer who were 18-64 years of age.
Exclusion criteria	Patients with a body mass index (BMI).30, significant arrhythmias, cardiopulmonary dysfunction, extensive peripheral arterial occlusive disease, significant renal or liver diseases, pregnancy or lactation and coagulopathy were excluded.
Age, gender and ethnicity	Age - Mean (SD): 56.7 ±6.9 GD-RL, 52.8 ±11.8 GD-C, 53.3±13.0 R-RL . Gender (M:F): 42/18.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation:
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Colloid - Starches. a fixed infusion of 4 ml/kg per hour of lactated Ringer's solution throughout the operation. In addition, this group received 250 ml of 6% hydroxyethyl starch (HES, 130/0.4) as a bolus in 15 minutes if the PPV was 11%.. Duration 183.0 ± 13.8 mins. Concurrent medication/care: Anesthesia was maintained with a 2.5-3% concentration of sevoflurane in O2, and fentanyl and vecuronium were administered intermittently for intraoperative analgesia and muscle relaxation. Immediately after induction, all of the patients received 2.0 g of cefazolin intravenously as an antibiotic prophylaxis. The body temperature was maintained over 36˚C with a fluid warmer throughout surgery. All of the surgeries in this study were performed by the same surgical team. Intraoperative 4 ml/kg/h lactated Ringer's solution was infused continuously at a constant rate via an infusion pump (TOP-3300H, TOP Corporation, Japan). The mean arterial pressure was maintained within ¡20% of the baseline value during the operation. Blood loss was replaced with HES at a 1:1 ratio, and the blood transfusion was started when clinically indicated and supported by laboratory evidence of a hematocrit less than 28%. Indirectness: No indirectness. (n=20)

	Intervention 2: Crystalloid - Lactated Ringer's (USP). The goal-directed Ringer's lactate (GD-RL) group received a fixed infusion of 4 ml/kg per hour of lactated Ringer's solution throughout the operation. In addition, this group received 250 ml of lactated Ringer's solution as a bolus in 15 minutes if the PPV was >11%. The restrictive Ringer's lactate (R-RL) group (n=20) received a fixed infusion of 4 ml/kg per hour of lactated Ringer's solution exclusively throughout the operation. The PPV was not measured in the R-RL group. If the urine output was continuously, 0.5 ml/kg/h over two hours or the CVP was less than 4 mmHg, 250-ml boluses of lactated Ringer's solution were administered until these targets were restored.. Duration 190.3 ± 40.2. Concurrent medication/care: Anesthesia was maintained with a 2.5-3% concentration of sevoflurane in O2, and fentanyl and vecuronium were administered intermittently for intraoperative analgesia and muscle relaxation. Immediately after induction, all of the patients received 2.0 g of cefazolin intravenously as an antibiotic prophylaxis. The body temperature was maintained over 36˚C with a fluid warmer throughout surgery. All of the surgeries in this study were performed by the same surgical team. Intraoperative 4 ml/kg/h lactated Ringer's solution was infused continuously at a constant rate via an infusion pump (TOP-3300H, TOP Corporation, Japan). The mean arterial pressure was maintained within ¡20% of the baseline value during the operation. Blood loss was replaced with HES at a 1:1 ratio, and the blood transfusion was started when clinically indicated and supported by laboratory evidence of a hematocrit less than 28%.. Indirectness: No indirectness. Comments: goal directed ringers lactate plus restrictive ringers lactate will be grouped together
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STARCHES versus LACTATED RINGER'S (USP) Protocol outcome 1: Length of hospital stay - Actual outcome: length of hospital stay at Please enter a time period.; Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Adverse events and complications ; Unplanned ICU admission ; Length of stay in intensive care unit

Study	**Dawidson 1991[18]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in USA
Line of therapy	Unclear

Study	Dawidson 1991[18]
Duration of study	Intervention + follow up: 13 days hours postoperatively
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients undergoing abdominal aortic surgery.
Exclusion criteria	Not reported
Age, gender and ethnicity	Age - Mean (SD): 64 (12) . Gender (M:F): 11/9 Ethnicity (w/b): 12/8.
Further population details	1. Age: >60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Crystalloid - Lactated Ringers with dextran-60 during surgery and 24 hours post-operatively.. Indirectness: No indirectness (n=10) Intervention 2: Crystalloid - : Lactated Ringers during surgery and 24 hours post-operatively.. Indirectness: No indirectness
Funding	Not reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HARTMANN'S versus STARCHES Protocol outcome 1: Mortality - Actual outcome: Mortality at Unclear; Group 1: 1/10, Group 2: 1/10 Risk of bias: All domain – High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay - Actual outcome: Length of hospital stay at until discharge; Group1: (n=10) Mean (SD): 11 days (8), Group 2: (n=10) Mean (SD): 17 days (13), Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the	Quality of life ; Unplanned ICU admission ; Length of stay in intensive care unit; Complications

Study	Dawidson 1991[18]
study	

Study	Shackford 1983[69]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=58)
Countries and setting	Conducted in USA
Line of therapy	Unclear
Duration of study	Intervention + follow up: Duration of hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing abdominal aortic reconstruction.
Exclusion criteria	
Age, gender and ethnicity	Age - Mean (SD): 61 years (1.5) . Gender (M:F): Not reported .
Further population details	1. Age: >60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Crystalloid - Lactated Ringers, 130 mEq sodium/L, 274 mOsm/L) . Indirectness: No indirectness (n=30) Intervention 2: Crystalloid - Hypertonic balanced salt solution (HSL, 205 mEq sodium/L, 514 mOsm/L).. Indirectness: No indirectness
Funding	Not reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HARTMANN'S versus STARCHES

Protocol outcome 1: Mortality
- Actual outcome: Mortality at Unclear; Group 1: 1/30, Group 2: 1/28
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Shackford 1983[69]
Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events and complications - Actual outcome: Pulmonary complications at Unclear; Group 1: 0/30, Group 2: 0/28 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: Renal complications at Unclear; Group 1: 0/30, Group 2: 0/28 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Unplanned ICU admission ; Length of hospital stay; Length of stay in intensive care unit

Study	Waters 2001[83]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in USA
Line of therapy	Unclear
Duration of study	Intervention + follow up: Duration of hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing aortic reconstructive surgery.
Exclusion criteria	Patients were excluded from the study if the catheter did not function postoperatively.
Age, gender and ethnicity	Age - Mean (SD): 70 years (8) . Gender (M:F): not reproted.
Further population details	1. Age: >60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Crystalloid - Intraoperative Lactated ringers. Anaesthetic and fluid management were standardised. Indirectness: No indirectness

Study	Waters 2001[83]
	(n=33) Intervention 2: Crystalloid - Intraoperative normal saline. Anaesthetic and fluid management were standardised. Indirectness: No indirectness
Funding	Supported, in part, by a grant sponsored by the I. H. Page Center for Health Outcomes Research.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HARTMANN'S versus STARCHES Protocol outcome 1: Mortality - Actual outcome: Mortality at Unclear; Group 1: 1/33, Group 1: 5/33 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events and complications - Actual outcome: Sepsis at Unclear; Group 1: 0/33, Group 1: 5/33 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Unplanned ICU admission ; Length of hospital stay; Length of stay in intensive care unit

Appendix E: Forest plots

E.1 Intravenous crystalloid versus colloid

Figure 2: Mortality

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Feldheiser 2013	0	24	5	24	28.5%	0.09 [0.01, 1.56]
Joosten 2018	3	80	0	80	27.4%	7.00 [0.37, 133.36]
Yates 2014	2	98	5	104	44.1%	0.42 [0.08, 2.14]
Total (95% CI)		**202**		**208**	**100.0%**	**0.59 [0.07, 4.81]**
Total events	5		10			

Heterogeneity: Tau² = 1.92; Chi² = 4.51, df = 2 (P = 0.11); I² = 56%
Test for overall effect: Z = 0.49 (P = 0.62)

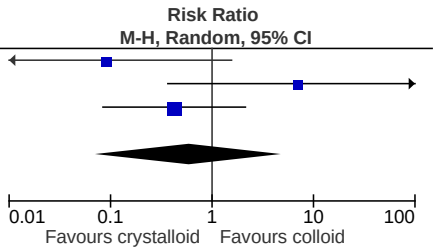


Figure 3: Compilation: Any major complication

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Joosten 2018	23	80	9	80	48.0%	2.56 [1.26, 5.17]
Yates 2014	19	98	26	104	52.0%	0.78 [0.46, 1.31]
Total (95% CI)		**178**		**184**	**100.0%**	**1.37 [0.43, 4.44]**
Total events	42		35			

Heterogeneity: Tau² = 0.62; Chi² = 7.13, df = 1 (P = 0.008); I² = 86%
Test for overall effect: Z = 0.53 (P = 0.60)

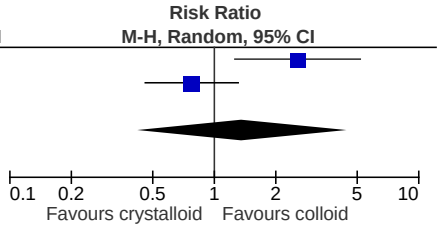


Figure 4: Compilation: Acute kidney injury

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Joosten 2018	23	80	19	80	50.7%	1.21 [0.72, 2.04]
Werner 2018	13	20	24	32	49.3%	0.87 [0.59, 1.27]
Total (95% CI)		**100**		**112**	**100.0%**	**1.04 [0.75, 1.45]**
Total events	36		43			

Heterogeneity: Chi² = 1.22, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 0.24 (P = 0.81)

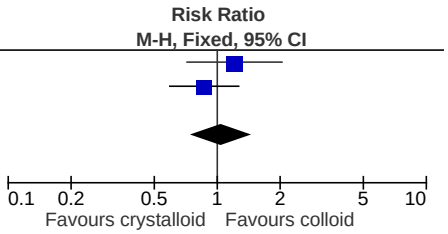


Figure 5: Compilation: Nausea and vomiting

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Nausea and vomiting						
Joosten 2018	33	80	28	80	58.7%	1.18 [0.79, 1.75]
Subtotal (95% CI)		**80**		**80**	**58.7%**	**1.18 [0.79, 1.75]**
Total events	33		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
1.4.2 Vomiting						
Zhang 2012	5	20	3	20	6.3%	1.67 [0.46, 6.06]
Subtotal (95% CI)		**20**		**20**	**6.3%**	**1.67 [0.46, 6.06]**
Total events	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.44)						
1.4.3 Nausea						
Moretti 2003	22	30	25	60	35.0%	1.76 [1.22, 2.55]
Subtotal (95% CI)		**30**		**60**	**35.0%**	**1.76 [1.22, 2.55]**
Total events	22		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.00 (P = 0.003)						
Total (95% CI)		**130**		**160**	**100.0%**	**1.41 [1.08, 1.85]**
Total events	60		56			
Heterogeneity: Chi² = 2.23, df = 2 (P = 0.33); I² = 10%						
Test for overall effect: Z = 2.49 (P = 0.01)						
Test for subgroup differences: Chi² = 2.14, df = 2 (P = 0.34), I² = 6.6%						

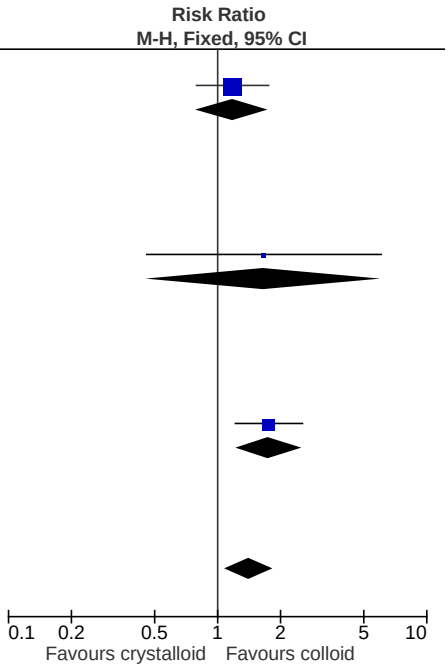


Figure 6: Compilation: Pulmonary complication

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Random, 95% CI
Abdallah 2014	2	22	1	22	13.4%	2.00 [0.20, 20.49]
Joosten 2018	14	80	4	80	29.1%	3.50 [1.20, 10.17]
Shah 2014	2	40	1	40	13.1%	2.00 [0.19, 21.18]
Yates 2014	11	98	20	104	35.7%	0.58 [0.30, 1.15]
Zhang 2012	1	20	0	20	8.6%	3.00 [0.13, 69.52]
Total (95% CI)		**260**		**266**	**100.0%**	**1.57 [0.56, 4.40]**
Total events	30		26			
Heterogeneity: Tau² = 0.65; Chi² = 8.83, df = 4 (P = 0.07); I² = 55%						
Test for overall effect: Z = 0.86 (P = 0.39)						

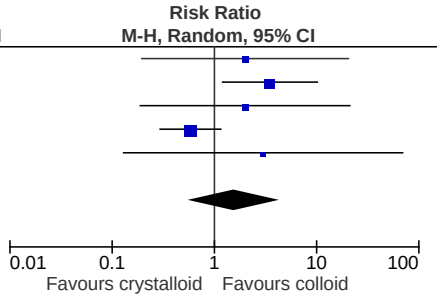


Figure 7: Compilation: Wound infection

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Joosten 2018	6	80	5	80	83.3%	1.20 [0.38, 3.77]
Zhang 2012	1	20	1	20	16.7%	1.00 [0.07, 14.90]
Total (95% CI)		**100**		**100**	**100.0%**	**1.17 [0.41, 3.35]**
Total events	7		6			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						

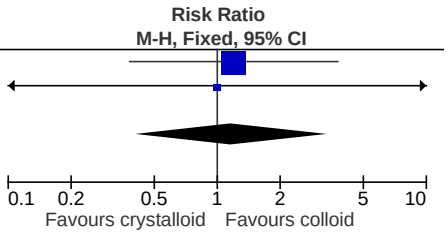


Figure 8: Compilation: Highest grade of compilation – Calviend Dindo I

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Feldheiser 2013	0	24	6	24	100.0%	0.08 [0.00, 1.29]
Total (95% CI)		**24**		**24**	**100.0%**	**0.08 [0.00, 1.29]**
Total events	0		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.78 (P = 0.07)

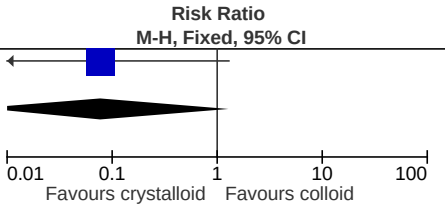


Figure 9: Compilation: Highest grade of compilation – Clavien Dindo II

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Feldheiser 2013	15	24	9	24	100.0%	1.67 [0.91, 3.04]
Total (95% CI)		**24**		**24**	**100.0%**	**1.67 [0.91, 3.04]**
Total events	15		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)

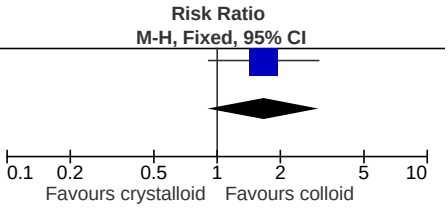


Figure 10: Compilation: Highest grade of compilation – Clavien Dindo IIIa

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Feldheiser 2013	1	24	1	24	100.0%	1.00 [0.07, 15.08]
Total (95% CI)		**24**		**24**	**100.0%**	**1.00 [0.07, 15.08]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

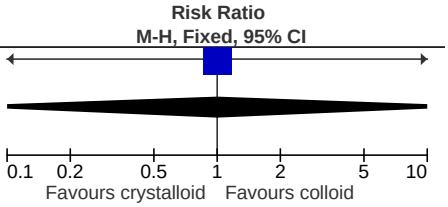


Figure 11: Compilation: Highest grade of compilation – Clavien Dindo IIIb

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Feldheiser 2013	3	24	5	24	100.0%	0.60 [0.16, 2.23]
Total (95% CI)		**24**		**24**	**100.0%**	**0.60 [0.16, 2.23]**
Total events	3		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)

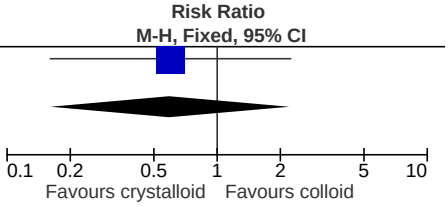


Figure 12: Compilation: Highest grade of compilation – Clavien Dindo IVa

Study or Subgroup	Crystalloid Events	Crystalloid Total	Colloid Events	Colloid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Feldheiser 2013	0	24	2	24	100.0%	0.20 [0.01, 3.96]
Total (95% CI)		**24**		**24**	**100.0%**	**0.20 [0.01, 3.96]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)

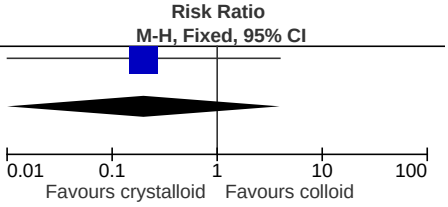
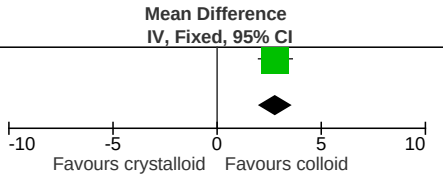


Figure 13: Length of hospital stay

Study or Subgroup	Crystalloid Mean	SD	Total	Colloid Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zhang 2012	11.9	1.2	20	9.1	1.4	20	100.0%	2.80 [1.99, 3.61]
Total (95% CI)			**20**			**20**	**100.0%**	**2.80 [1.99, 3.61]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.79 (P < 0.00001)



E.2 Crystalloid within class comparison

E.2.1 Lactated Ringer's versus normal saline

Figure 14: Mortality

Study or Subgroup	Sodium lactated ringers Events	Total	Sodium normal saline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Waters 2001	1	33	1	33	100.0%	1.00 [0.07, 15.33]
Total (95% CI)		**33**		**33**	**100.0%**	**1.00 [0.07, 15.33]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

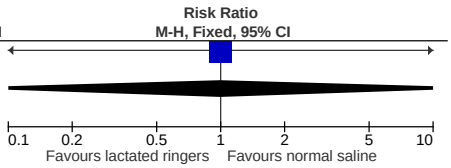
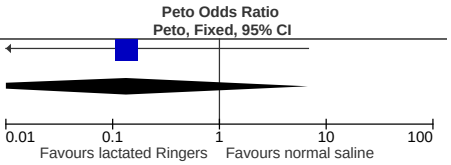


Figure 15: Infection (sepsis)

Study or Subgroup	Sodium lactated ringers Events	Total	Sodium normal saline Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Waters 2001	0	33	1	33	100.0%	0.14 [0.00, 6.82]
Total (95% CI)		**33**		**33**	**100.0%**	**0.14 [0.00, 6.82]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)



E.2.2 Lactated Ringer's (+ 3% dextrose) versus Lactated Ringer's

Figure 16: Mortality

Study or Subgroup	Lactated ringers + dex Events	Total	Lactated ringers Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dawidson 1991	1	10	1	10	100.0%	1.00 [0.07, 13.87]
Total (95% CI)		**10**		**10**	**100.0%**	**1.00 [0.07, 13.87]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

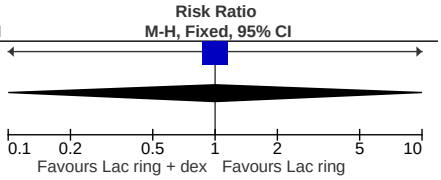
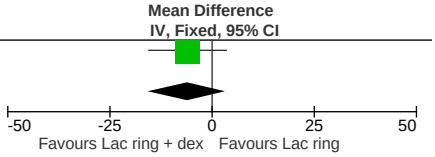


Figure 17: Length of hospital stay

Study or Subgroup	Lactated ringers + dex Mean	SD	Total	Lactated ringers Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Dawidson 1991	11	8	10	17	13	10	100.0%	-6.00 [-15.46, 3.46]
Total (95% CI)			**10**			**10**	**100.0%**	**-6.00 [-15.46, 3.46]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.21)



E.2.3 Hypertonic balanced salt versus Lactated Ringer's

Figure 18: Mortality

Study or Subgroup	HSL Events	HSL Total	LR Events	LR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Shackford 1983	1	30	1	28	100.0%	0.93 [0.06, 14.22]
Total (95% CI)		**30**		**28**	**100.0%**	**0.93 [0.06, 14.22]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)

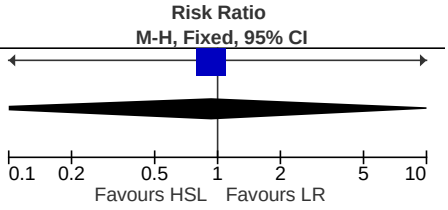


Figure 19: Complication – Pulmonary

Study or Subgroup	HSL Events	HSL Total	LR Events	LR Total	Weight	Risk Difference M-H, Fixed, 95% CI
Shackford 1983	0	30	0	28	100.0%	0.00 [-0.06, 0.06]
Total (95% CI)		**30**		**28**	**100.0%**	**0.00 [-0.06, 0.06]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

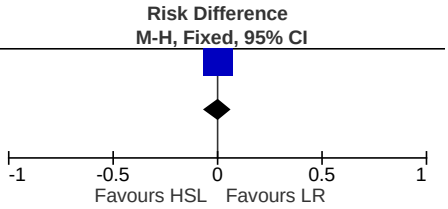
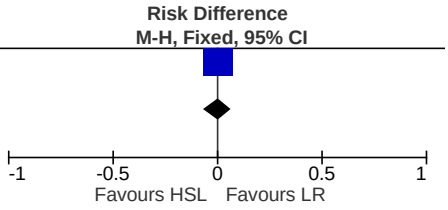


Figure 20: Complication – Renal failure

Study or Subgroup	HSL Events	HSL Total	LR Events	LR Total	Weight	Risk Difference M-H, Fixed, 95% CI
Shackford 1983	0	30	0	28	100.0%	0.00 [-0.06, 0.06]
Total (95% CI)		**30**		**28**	**100.0%**	**0.00 [-0.06, 0.06]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Appendix F: GRADE tables

Table 14: Clinical evidence profile: Intravenous crystalloid versus intravenous colloid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Crystalloid versus colloid	Control	Relative (95% CI)	Absolute		
Mortality (1 to 3 months) (follow-up 1-3 months)												
3	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[2]	none	5/202 (2.5%)	4.8%	RR 0.59 (0.07 to 4.81)	20 fewer per 1000 (from 45 fewer to 183 more)	⊕OOO VERY LOW	CRITICAL
Complication: (patients with major complication)												
2	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	very serious[2]	none	42/178 (23.6%)	18.1%	RR 1.37 (0.43 to 4.44)	67 more per 1000 (from 103 fewer to 623 more)	⊕OOO VERY LOW	CRITICAL
Complication: Acute kidney injury												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	36/100 (36%)	49.4%	RR 1.04 (0.75 to 1.45)	20 more per 1000 (from 124 fewer to 222 more)	⊕⊕OO LOW	CRITICAL
Complication: Nausea and vomiting												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	60/130 (46.2%)	35%	RR 1.41 (1.08 to 1.85)	143 more per 1000 (from 28 more to 298 more)	⊕⊕⊕O MODERATE	CRITICAL
Complication: Nausea and vomiting - Nausea and vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	33/80 (41.3%)	35%	RR 1.18 (0.79 to 1.75)	63 more per 1000 (from 73 fewer to 262 more)	⊕⊕OO LOW	CRITICAL

Complication: Nausea and vomiting - Vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/20 (25%)	15%	RR 1.67 (0.46 to 6.06)	100 more per 1000 (from 81 fewer to 759 more)	⊕⊕OO LOW	CRITICAL
Complication: Nausea and vomiting - Nausea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	22/30 (73.3%)	41.7%	RR 1.76 (1.22 to 2.55)	317 more per 1000 (from 92 more to 646 more)	⊕⊕⊕O MODERATE	CRITICAL
Complication: Pulmonary												
5	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[1]	none	30/260 (11.5%)	4.6%	RR 1.57 (0.56 to 4.40)	26 more per 1000 (from 20 fewer to 156 more)	⊕OOO VERY LOW	CRITICAL
Complication: Wound infection												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7/100 (7%)	5.6%	RR 1.17 (0.41 to 3.35)	10 more per 1000 (from 33 fewer to 132 more)	⊕⊕OO LOW	CRITICAL
Complications: Clavien-Dindo grade I (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/24 (0%)	25%	RR 0.08 (0 to 1.29)	230 fewer per 1000 (from 250 fewer to 72 more)	⊕⊕OO LOW	CRITICAL
Complications: Clavien-Dindo grade II (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	15/24 (62.5%)	37.5%	RR 1.67 (0.91 to 3.04)	251 more per 1000 (from 34 fewer to 765 more)	⊕⊕⊕O MODERATE	CRITICAL
Complications: Clavien-Dindo grade IIIa (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/24 (4.2%)	4.2%	RR 1 (0.07 to 15.08)	0 fewer per 1000 (from 39 fewer to 591 more)	⊕⊕OO LOW	CRITICAL
Complications: Clavien-Dindo grade IIIb (follow-up 3 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/24 (12.5%)	20.8%	RR 0.6 (0.16 to 2.23)	83 fewer per 1000 (from 175 fewer to 256 more)	⊕⊕OO LOW	CRITICAL
Complications: Clavien-Dindo grade IVa (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/24 (0%)	8.3%	RR 0.2 (0.01 to 3.96)	66 fewer per 1000 (from 82 fewer to 246 more)	⊕⊕OO LOW	CRITICAL
Length of hospital stay (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 2.8 higher (1.99 to 3.61 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Downgraded by 1 or 2 increments because heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 15: Clinical evidence profile: Lactated Ringer's compared to normal saline for perioperative care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lactated Ringer's**	**Normal saline**	**Relative (95% CI)**	**Absolute**		
Mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/33 (3%)	3%	RR 1 (0.07 to 15.33)	0 fewer per 1000 (from 28 fewer to 430 more)	⊕⊕OO LOW	CRITICAL
Infection (sepsis)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/33 (0%)	3%	Peto OR 0.14 (0 to 6.82)	26 fewer per 1000 (from 30 fewer to 175 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 16: Clinical evidence profile: Lactated Ringer's (+ 3% dextrose) compared to Lactated Ringer's for perioperative care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactated Ringer's (+ 3% dextrose)	Lactated Ringer's	Relative (95% CI)	Absolute		
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/10 (10%)	10%	RR 1 (0.07 to 13.87)	0 fewer per 1000 (from 93 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10	10	-	MD 6 lower (15.46 lower to 3.46 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence profile: Hypertonic balanced salt compared to Lactated Ringer's for perioperative care

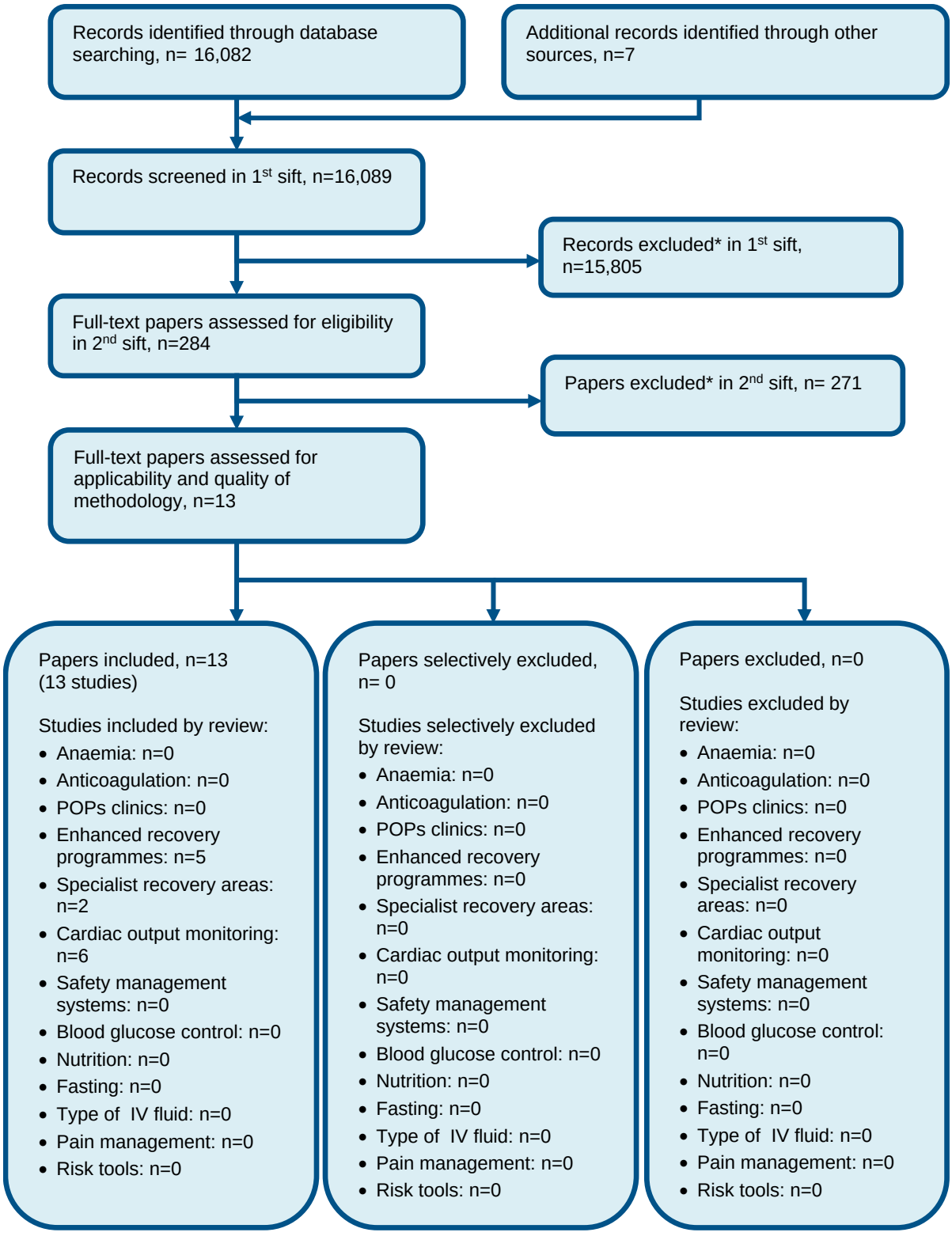
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypertonic balanced salt	Lactated Ringer's	Relative (95% CI)	Absolute		
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/30 (3.3%)	3.6%	RR 0.93 (0.06 to 14.22)	3 fewer per 1000 (from 34 fewer to 476 more)	⊕OOO VERY LOW	CRITICAL
Complication: Pulmonary												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/30 (0%)	0%	RD 0.00 (-0.06 to 0.06)	-	⊕⊕OO LOW	CRITICAL

Complication: Renal failure												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/30 (0%)	0%	RD 0 (-0.06 to 0.06)	-	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection

Figure 21: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 18: Studies excluded from the clinical review

Reference	Reason for exclusion
Ahmed 2017[2]	Inappropriate intervention
Ahn 2008[3]	Colloids not recommended - within class comparison
Al-Ghamdi 2018[4]	Inappropriate study design
Auler Jr 1987[5]	No relevant outcome
Awad 2012[6]	Inappropriate comparison
Azuma 1994[7]	Not in English
Beyer 1997[8]	Colloids not recommended - within class comparison
Billiodeaux 2014[9]	No relevant outcome
Boldt 2003[10]	Inappropriate study design
Boldt 2007[11]	Colloids not recommended - within class comparison
Brandstrup 2006[12]	Inappropriate study design
Campbell 1990[13]	No relevant outcome
Chin 2006[14]	No relevant outcome
Choi 2010[15]	Colloids not recommended - within class comparison
Cook 1990[16]	No relevant outcome
Cyna 2006[17]	Inappropriate intervention
Demirel 2018[19]	Inappropriate intervention
Deng 2017[20]	No relevant outcome
Eng 2017[21]	Inappropriate study design
Gan 2002[25]	Inappropriate intervention
Gan 1999[24]	Colloids not recommended - within class comparison
Gandhi 2007[26]	Colloids not recommended - within class comparison
Gold 1990[27]	Colloids not recommended - within class comparison
Gómez-Izquierdo 2017[28]	Inappropriate intervention
Grant 2013[29]	Inappropriate study design
Groeneveld 2011[30]	Inappropriate Systematic review, references screened.
Hamaji 2013[31]	Inappropriate intervention
Hasan 2012[32]	Inappropriate intervention
Heinze 2009[33]	Colloids not recommended - within class comparison
Helmy 2016[34]	Colloids not recommended - within class comparison
Heming 2018[35]	Inappropriate intervention
Hesler 2015[36]	Inappropriate study design
Hiippala 1996[37]	No relevant outcome
Holte 2007[38]	Inappropriate intervention

Reference	Reason for exclusion
Jover 2009[41]	Not in English
Jungheinrich 2004[42]	Colloids not recommended - within class comparison
Kammerer 2018[43]	Colloids not recommended - within class comparison
Kashy 2014[44]	Inappropriate study design
Kulla 2008[45]	Not available
Lang 2001[46]	Inappropriate Article retracted
Langeron 2001[47]	Colloids not recommended - within class comparison
Lee 2003[49]	Not in English
Lee 2004[48]	Not in English
Leone Roberti Maggiore 2014[50]	Inappropriate intervention
Lewis 2016[51]	Inappropriate Systematic review, references screened.
Li 2013[52]	Colloids not recommended - within class comparison
Magner 2004[53]	Inappropriate intervention
McFarlane 1994[54]	No relevant outcome
Mittermayr 2008[55]	No relevant outcome
Mittermayr 2007[56]	Colloids not recommended - within class comparison
Mortelmans 1995[58]	Colloids not recommended - within class comparison
Mukhtar 2009[59]	Colloids not recommended - within class comparison
Noblett 2006[62]	Inappropriate intervention
Prien 1990[63]	No relevant outcome
Rollins 2016[64]	Inappropriate intervention
Ruttmann 2002[65]	No relevant outcome
Sander 2003[66]	Colloids not recommended - within class comparison
Sawada 2016[67]	No relevant outcome
Schol 2016[68]	Inappropriate intervention
Sieber 1986[71]	Inappropriate population
Sinclair 1997[72]	Inappropriate intervention
Soares 2009[73]	Inappropriate population
Tellan 2008[75]	Not in English
Tigchelaar 1998[76]	Inappropriate population
Tormann 1990[77]	Not in English
Van Der Linden 2013[78]	Inappropriate Systematic review, references screened.
Venn 2002[79]	Inappropriate intervention
Walsh 1983[80]	No relevant outcome
Wang 2018[82]	Inappropriate intervention
Wang 2015[81]	Inappropriate population
Wool 2010[85]	Inappropriate intervention
Yamasaki 2010[86]	No relevant outcome
Yokoyama 2008[88]	No relevant outcome

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 19: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	