National Institute for Health and Care Excellence

Consultation

Perioperative care in adults

[J] Non-invasive cardiac output monitoring

NICE guideline

Intervention evidence review

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Draft for Consultation

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1 Non-invasive cardiac output monitoring

1.1 Review question: What is the clinical and cost effectiveness of non-invasive cardiac output monitoring during surgery in adults?

1.2 Introduction

Cardiac output monitoring has been a part of perioperative practice for a number of years, primarily used to achieve fluid optimisation and guide the use of vasoactive and inotropic drugs for patients undergoing major surgery. More recently there has been a trend towards less liberal fluid management and the use of goal-directed fluid therapy, based on cardiac output monitoring.

In light of recent changes to practice, this section looks at the evidence for the most clinical and cost-effective strategies for the use of non-invasive cardiac monitoring, with consideration of the benefits and risks of the various available monitors being considered.

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 major or complex or high risk surgery (based on NICE preoperative tests for elective surgery guideline categorisation) and high risk patients (based on American Society of Anesthesiologists physical status grade) undergoing any surgery.

Interventions	• non-invasive cardiac output monitoring
	  ○ oesophageal doppler monitor
	  ○ trans-oesophageal echocardiography
	  ○ thoracic electrical bioimpedance
	  ○ pulse pressure waveform analysis
	  ○ systems based on pulse contour analysis and dye dilution

Comparisons	• pulmonary artery catheter • conventional clinical assessment
Outcomes	Critical outcomes: • health-related quality of life • mortality • perioperative complications Important outcomes: • length of hospital stay • length of stay in intensive care unit • hospital readmission
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. Prospective cohort studies if no RCT evidence is identified.

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1.4 Clinical evidence

1.4.1 Included studies

Twenty-three randomly controlled trials were included in the review[3, 22, 24, 28, 36, 40, 43, 53, 59, 67, 71, 76, 80, 81, 84, 87, 88, 91, 93, 94, 100, 101, 108] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). 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.

One study compared oesophageal Doppler monitoring to pulse contour analysis and the remaining twenty-two studies compared cardiac output monitoring to conventional clinical assessment. Non-invasive cardiac output monitoring interventions were grouped for this comparison to assess the overall efficacy of non-invasive cardiac output monitoring interventions. Subgroup analysis would explore differences between intervention methods if heterogeneity it outcome data was observed.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bartha 2013[3]	**Pulse contour analysis:** Fluid challenge (3 ml kg21) with colloid administered and repeated if a 10% increase in stroke volume achieved. If no increase occurred, and if oxygen delivery was, 600 ml min21m22, then a dobutamine infusion was started at 0.2–10 mgkg21 min21. The infusion was stopped if tachycardia occurred. Further fluid challenges were given if the SV decreased by 10%. The research team administered GDT, which was discontinued at the end of the operation. N=70 **Conventional clinical assessment:** The attending anaesthesia team managed the routine fluid treatment. Colloids were administered before spinal anaesthesia followed by the background infusion of buffered glucose and Ringer's acetate according to the treatment algorithm. Other fluids or vasopressor treatment (e.g. phenylephrine and	Patients aged ≥70 years and weight ≥40 kg who were undergoing proximal femoral fracture surgery. Median age (range): 85 years (71-101) Sweden	• Length of hospital stay • Complications	All patients were monitored with a lithium dilution cardiac output monitor (LiDCO). The LiDCO monitor was covered for the attending anaesthesia team.

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Study	Intervention and comparison	Population	Outcomes	Comments
	ephedrine) for correction of decreasing arterial pressure were administered at the attending anaesthetist's discretion. N=75			
Correa-Gallego 2015[22]	**Pulse contour analysis:** At the completion of transection goal directed fluid management was initiated following an algorithm using a FloTrac monitor; 1:1 blood loss replacement with colloid, and albumin bolus infusions to restore SVV to a value ≤ 2 standard deviations from their baseline after induction. Crystalloid infusion was continued at 1ml/kg/hr. N=69 **Conventional clinical assessment:** Standard fluid management; 1:1 blood loss replacement with colloid, and crystalloid infusion at 6 ml/kg/hr of total operative time to restore the calculated insensible losses and maintenance requirements. N=66	All adult patients scheduled to undergo an open, elective liver resection. Mean age (SD): 56.5 years (13.5) USA	• Mortality • Length of hospital stay • Readmission • Complications	All patients had continuous arterial waveform monitoring from the beginning of the operation and their SVV after induction was recorded using the FloTrac sensor and EV1000 clinical platform.
Dhawan 2018[24]	**Transesophageal echocardiography:** Patients had TEE used throughout the intraoperative period to assist with fluid and hemodynamic management.	Patients undergoing elective radical cystectomy for invasive bladder cancer. Mean age (SD): 67 (10)	• Mortality • Length of hospital stay • Complications	While TEE was not routinely used in this group, it was allowed if requested by the general anaesthesiologist during the intraoperative period in a "rescue" role to evaluate life-threatening

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Study	Intervention and comparison	Population	Outcomes	Comments
	N=38 **Conventional clinical assessment:** Standardized general anaesthetic with radial artery blood pressure monitoring. N=39	USA		hemodynamic instability.
Feldheiser 2015[28]	**Oesophageal Doppler monitoring:** CardioQ-ODM shown to the treating personnel and the goal-directed algorithm was performed according to the values measured by the ODM. N=11 **Pulse contour analysis:** LiDCOrapid was shown to the treating personnel and the algorithm was performed according to the values measured by the LiDCO. N=10 The goal-directed algorithm guides the administration of intravenous colloid solution to maintain preload, the titration of norepinephrine to maintain arterial blood pressure and if necessary the titration of enoximone or nitroglycerine to lower central venous pressure.	Patients aged at least 18 years and undergoing elective liver resection (hemihepatectomy or extended liver resection). Median age (IQR): ODM: 69 years (56-75) PPA: 52 years (41-65) Germany	• Length of hospital stay • Complications	Conventional care arm implemented in study; due to an unbalance in the extension of the surgical procedures with a high rate of only minor procedures the conventional group was dropped from the analysis. In each of the three allocation groups both the ODM and PPA were established. ASA ≥IV excluded
Hand 2016[36]	**Pulse contour analysis:** Goal-directed haemodynamic	All patients scheduled for primary free tissue transfer	• Length of hospital stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
	therapy using Vigileo and EV-1000. Measures BP, SV variation, cardiac index, and systemic vascular resistance via central line. Hypotension defined as man arterial pressure <75mm Hg or >10% below baseline. Treatment algorithm dictates no action or treatment with IVF bolus, dobutamine, epinephrine or phenylephrine. N=47 **Conventional clinical assessment:** Standard management of hypotension, utilising only IV fluids (crystalloid and colloid). Goal BP was set as mean arterial pressure >70 or within 20% of baseline. N=47	reconstruction with head and neck oncologic surgeons were enrolled. Mean age (SD): 58.4 years (13) USA	• Length of stay in ICU • Complications	
Kapoor 2016[40]	**Pulse contour analysis:** Goal-directed haemodynamic therapy. Received standard haemodynamic monitoring. In addition, the cardiac index and the continuous central venous oxygen saturation were monitored. A cardiac output monitoring sensor was connected to the radial arterial cannula. If the CI was <2.5 L/min/m2, CVP <6 mmHg, or SVV >10%, fluids were given	Patients with a European system for cardiac operative risk evaluation ≥3 undergoing coronary artery bypass grafting. Mean age (SD): 61.2 years (5.4) India	• Mortality • Length of hospital stay • Length of stay in ICU	

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Study	Intervention and comparison	Population	Outcomes	Comments
	intravenously until the target CVP and SVV levels were achieved. N=60 **Conventional clinical assessment:** Received standard haemodynamic monitoring including Electrocardiogram oxygen saturation, invasive blood pressure, central venous pressure and arterial blood gas, urine output, and $EtCO_2$ monitoring were common to both the groups. All patients received fluids to maintain the CVP between 6 and 8 mmHg and MAP was maintained between 90 and 105 mmHg using inotropic agents and vasodilators. N=60			
Lai 2015[43]	**Pulse contour analysis:** Goal-directed haemodynamic therapy. A medically qualified investigator monitored patients throughout surgery with a LiDCOrapid. The concealed investigator administered warmed colloid fluid challenges with Gelofusine directed by an algorithm to achieve an SVV goal of less than 10% throughout surgery.	Patients having major elective rectal resection or cystectomy with ileal conduit. Mean age (SD): 63 years (15) UK	• Mortality • Complications • Length of hospital stay • Readmission	

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Study	Intervention and comparison	Population	Outcomes	Comments
	N= 110 **Conventional clinical assessment:** All patients received mechanical ventilation whilst under general anaesthesia; tidal volume was not protocolised. The anaesthetist administered intraoperative crystalloid, colloid, blood products, and inotropes or vasopressors based on estimated patient requirements, losses, and standard haemodynamic variables. All participants had arterial line monitoring. Central venous pressure monitoring was permitted. Standard fluid therapy was not defined, but a general recommendation was made that perioperative fluid excess should be avoided. N= 111			
Mayer 2010[53]	**Pulse contour analysis:** Standard monitoring plus enhanced hemodynamic monitoring with the FloTrac/Vigileo device and an attempted cardiac index of at least 2.5 L·min-1·m-2. The arterial line was connected to the Vigileo monitor via the FloTrac pressure transducer. The shape of the arterial curve	Patients with an ASA status of III with two or more risk factors undergoing open major abdominal surgery (intestine resection, gastric resection, liver resection, esophageal resection, Whipple). Mean age (range): 72.5	• Mortality • Complications • Length of hospital stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
	was checked visually for damping throughout the study period. CI, stroke volume index (SVI), as an indicator for fluid status, and stroke volume variation, (SVV) as an indicator for fluid responsiveness during mechanical ventilation and sinus rhythm, were continuously measured. Blood loss was substituted with crystalloid/colloid fluids according to an algorithm and a haemoglobin value below 8 mg dL-1 was considered to be a trigger for transfusion of packed red blood cells. N= 30 **Conventional clinical assessment:** Standard monitoring included electrocardiogram, invasive arterial blood pressure via right or left radial artery, CVP, pulse oximetry, temperature, inspiratory and expiratory gas concentrations. Crystalloid/ colloid delivered to ensure MAP was kept between 65 and 90 mmHg, CVP between 8 and 12 mmHg and urinary output more than 0.5 mL kg-1 h-1. N= 30	years (68-78) USA		
Moppett 2015[59]	**Pulse contour analysis:** A	Patients admitted through	• Mortality	

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Study	Intervention and comparison	Population	Outcomes	Comments
	LiDCO monitor was attached and calibrated, the use of vasoactive agents was at the discretion of the attending anaesthetist, as was target arterial pressure during surgery. Also received targeted i.v. colloid boluses using invasive pulse contour analysis continuous cardiac output monitoring to optimize SV following a predetermined algorithm. The attending anaesthetist was aware of the fluids being given. N=68 **Conventional clinical assessment:** A LiDCO monitor was attached and calibrated, the use of vasoactive agents was at the discretion of the attending anaesthetist, as was target arterial pressure during surgery. Operative anaesthetists were not allowed to view the LiDCO monitor for patients in the control group unless they believed that there was a strong clinical need to do so. N=62	the emergency department with primary fragility hip fracture, aged over 60 who were listed for surgical repair under spinal anaesthesia. Median age (range): 85 years (63-95) UK	• Complication • Length of hospital stay	
Noblett 2006[67]	**Oesophageal Doppler monitoring:** Routine perioperative monitoring. Crystalloid, colloid or blood	Consecutive patients undergoing colorectal resection.	• Mortality • Complication • Length of hospital stay	All patients had oesophageal Doppler monitors, but fluid administration for the intervention group was based solely on the

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Study	Intervention and comparison	Population	Outcomes	Comments
	products administered by the anaesthetist based on intraoperative losses and standard parameters. Received an additional colloid (Volpex) bolus to maintain a descending aortic corrected flow time of more than 0.35 seconds and further bolus given to optimise the stroke volume. Further bolus only given if SV fell by >10% or FTc fell below 0.35 seconds. N=54 **Conventional clinical assessment:** Routine perioperative monitoring included ECG, pulse oximetry, end-tidal carbon dioxide monitoring, and non-invasive BP monitoring. Crystalloid, colloid or blood products administered by the anaesthetist based on intraoperative losses and standard parameters. N=54	Mean age (SD): 64.9 years (14.6) UK	• Readmission	Doppler-assessed parameters, following a strict algorithm. Volpex administered by separate medically qualified reviewer to maintain blinding.
Pearse 2014[71]	**Pulse contour analysis:** Received intravenous fluid and inotropes according to a cardiac output–guided hemodynamic therapy algorithm using a cardiac output monitor (LiDCOrapid).	Patients aged 50 years or older undergoing major gastrointestinal surgery. Mean age (SD): 71.8 years (8.5)	• Mortality • Complications • Length of hospital stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
	Intravenous colloid solution was administered in 250mL boluses to achieve and maintain a maximal value of stroke volume. N=368 **Conventional Clinical assessment:** All patients received standard measures to maintain oxygenation, haemoglobin, core temperature, and HR. Additional fluid was administered at the discretion of the treating clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate, and base excess. N=366	UK		
Pillai 2011[76]	**Oesophageal Doppler monitoring:** Standard respiratory and cardiovascular monitoring including BP. Standard intraoperative fluids at the discretion of the consultant anaesthetists, and additional fluid from a researcher via esophageal Doppler determined protocol. Fluid given if SV increase by >10% and FTc <0.35 seconds N=32	Patients undergoing radical cystectomy as curative treatment for muscle invasive transitional cell carcinoma of the bladder. Mean age: 67.5 years UK	• Length of hospital stay • Complications	All patients had oesophageal Doppler inserted as to allow for double blinding.

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Study	Intervention and comparison	Population	Outcomes	Comments
	Conventional Clinical assessment: Standard respiratory and cardiovascular monitoring including BP. Standard intraoperative fluids at the discretion of the consultant anaesthetists. N=32			
Ramsingh 2013[80]	**Pulse contour analysis:** FloTrac/Vigileo system was used. GDT patients were managed by an SVV guided protocol to maintain SVV\12 %. N=18 **Conventional Clinical assessment:** Control patients had fluid management guided by routine cardiovascular monitoring at the discretion of their Staff Anesthesiologist, who was blinded to SVV data. N=20	Patients scheduled for major abdominal, non-vascular surgery. Mean age (SD): 59.2 years (16.9) USA	• Length of hospital stay	
Ratti 2016[81]	**Pulse contour analysis:** ECG and MAP were obtained using a radial or humeral catheterisation, pulse oxymetry and diuresis were monitored. Arterial access was connected to the FloTrac sensor of the Vigileo monitor system to measure SVV. In this group SV, CO and CI were monitored; VO2 and DO2 were calculated	Patients scheduled for laparoscopic liver resection (LLR) for primary or secondary liver tumours. Mean age (SD): 59.5 years (10) Italy	• Morbidity • Length of hospital stay • Complications	

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Study	Intervention and comparison	Population	Outcomes	Comments
	on the basis of blood gas analysis. The goal was to maintain SVV over 12% during resection. Fluid therapy with crystalloids was guided by SVV values to achieve a hypovolaemic state. N=45 **Conventional Clinical assessment:** ECG and MAP were obtained using a radial or humeral catheterization, pulse oxymetry and diuresis were monitored. CVP was measured through a CVC inserted in the internal jugular vein after the induction of general anaesthesia. In this group SvO2 was monitored as well. The goal was to maintain CVP under or equal to 5 cm H20. Fluid therapy with crystalloids was guided by CVP values to achieve a hypovolaemic state. N=45			
Salzwedel 2013[84]	**Pulse contour analysis: Conventional Clinical assessment:** Received basic anaesthetic monitoring. Additionally, hemodynamic therapy was guided by a predetermined algorithm accounting for pulse pressure variation, cardiac index trending and mean arterial	Patients undergoing elective abdominal surgery including general, gynecological and urological surgery with anticipated duration of surgery of more than 120 minutes or an estimated blood loss of more than 20% of blood volume, ASA classification 2 or 3, and an	• Complications • Length of hospital stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
	pressure as measured by a cardiac index trending monitor (ProAQT). N=79 **Conventional Clinical assessment:** Received basic anaesthetic monitoring by five-lead-electrocardiogram, pulse oximetry and blood pressure cuff, at least one peripheral i.v., a central venous catheter and invasive radial arterial blood pressure monitoring. Treatment was entirely performed at the discretion of the care-giving anaesthesiologist. N=81	indication for an arterial line and central venous catheter. Mean age (SD): 64 years (17.6) Germany		
Senagore 2009[87]	**Oesophageal Doppler monitoring:** Received standard anaesthesia and monitoring. A separate anaesthesia team administered Lactated Ringers bolus following an algorithm dictated by SVV. N=21 **Conventional Clinical assessment:** Received maintenance fluids based on clinical evaluation of the anaesthesia team, based on urinary outputs, HR increase, BP decrease, or CVP	Patients aged 18-90 years undergoing laparoscopic segmental colectomy. Age not reported USA	• Mortality • Complications • Length of hospital stay	Types of fluid administered for conventional care group included crystalloid or starch colloid. No breakdown of fluids given.

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Study	Intervention and comparison	Population	Outcomes	Comments
	decrease. N=22			
Shillcutt 2014[88]	**Trans-oesophageal echocardiography:** Echocardiography-guided hemodynamic management. Received hemodynamic management of crystalloid or colloid fluid based on left ventricular filling patterns on transesophageal echocardiography, according to a predetermined algorithm. N=14 **Conventional Clinical assessment:** Standard hemodynamic management using non-invasive blood pressure monitoring or invasive monitoring (arterial/central venous line) if so indicated by the anaesthetist. Target of keeping intraoperative BP within 10-15% of patient baseline readings. Fluids given as deemed appropriate by anaesthetist who were blinded to the study. N=14	Patients aged >65 years or aged >19 years with at least one risk factor for left ventricular diastolic dysfunction undergoing major non-cardiac surgery.	• Length of hospital stay	Type of surgery: • Orthopaedic: 9 • General: 12 • Vascular: 4 • Thoracic: 3
Smetkin 2009[91]	**Pulse contour analysis:** Advanced monitoring: Therapy	Patients diagnosed with coronary artery disease,	• Complications • Length of hospital stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
	targeted according to intrathorcic blood volume index, cardiac index (PICCOplus), HR, MAP, and central venous oxygen saturation. Colloid/anesthesia maintained according to predetermined algorithm. N=22 **Conventional Clinical assessment:** Conventional monitoring: hemodynamic and fluid management was primarily based on CVP, HR, and MAP. Colloid/anesthesia maintained according to predetermined algorithm. N=21	ranked ASA II-III, and scheduled for off-pump coronary artery bypass. Mean age (SD): 56.7 years (9.1) Russia	• Length of ICU stay	
Srinivasa 2013[93]	**Oesophageal Doppler monitoring:** Patients randomized to GDT were treated with a weight-based bolus of colloid, permitted based on cardiac function measured by means of an oesophageal Doppler monitor (CardioQ). An algorithm based on FTc and SV dictated fluid administration. N=37 **Conventional Clinical assessment:** Patients were allowed to receive up to 1500	Patients undergoing elective open or laparoscopic colectomy for any indication. Mean age (SD): 70.5 years (14) New Zealand	• Complications • Length of hospital stay • Readmissions	

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Study	Intervention and comparison	Population	Outcomes	Comments
	ml crystalloid solution during surgery. They were also permitted to receive a total of 500 ml succinylated gelatine colloid solution titrated by heart rate, blood pressure, urine output and invasive measures (arterial lines) when used. N=37			
Stens 2017[94]	**Pulse contour analysis:** Non-invasive continuous arterial blood pressure monitor was used for PPV and CI measurements in all patients. The anaesthetist was required to keep MAP > 70 mmHg, CI > 2.5 l min -1.m-2 and PPV < 12% using a predefined protocol. N=122 **Conventional Clinical assessment:** The attending anaesthetist was blinded to the PPV/CI values and maintained target MAP values > 70 mmHg (as measured by the Nexfin device) with intravenous fluids of any type, vasopressors and/or inotropes, based on their clinical judgement. N=122	Patients with elective moderate-risk abdominal surgery planned. Mean age (SD): 63 (12.5) The Netherlands	• Mortality • Complications • Length of hospital stay • Length of ICU stay • Readmissions	
Venn 2002[100]	**Oesophageal Doppler monitoring:** Patients received additional 200 ml gelofusine	Patients aged >65 years with fractured hips.	• Mortality • Complications • Length of hospital stay	CVP guided conventional care and conventional care groups were pooled for comparison with

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Study	Intervention and comparison	Population	Outcomes	Comments
	fluid challenges guided by Doppler measurements of stroke volume and corrected flow time from the investigator, in addition to any fluid given by the clinician. N=30 **Conventional Clinical assessment (CVP guided):** Patients received additional 200 ml gelofusine fluid challenges guided by the response of the central venous pressure to a fluid challenge from the investigator, in addition to any fluid given by the clinician. N=31 **Conventional Clinical assessment:** Clinicians were able to give i.v. fluid as they thought appropriate. Although central venous pressure was monitored and recorded by the investigator, the clinician was unaware of these measurements and so was unable to use them to guide therapy. The investigator gave no additional fluids in this group. N=29	Mean age (SD): 83.8 years (8.3) UK		oesophageal Doppler monitoring group.

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Study	Intervention and comparison	Population	Outcomes	Comments
	Intraoperatively, all patients received i.v. crystalloid (Hartmann's solution), colloid in the form of gelofusine, or blood to replace estimated and measured fluid losses, in an attempt to maintain heart rate and arterial pressure within 20% of pre-induction baseline levels.			
Wakeling 2005[101]	**Oesophageal Doppler monitoring:** In addition to routine fluid management, fluids adjusted according to ODM values following a predetermined algorithm. Patients received 250 ml boluses of colloid solution. If the stroke volume increased by 10% or more but the CVP did not rise by 3 mm Hg or more, the fluid challenge was repeated. The fluid challenges of 250 ml were repeated until the stroke volume failed to rise by 10% and/or the CVP rose by 3 mm Hg or more. No further colloid fluid boluses were given until a 10% decrease in stroke volume occurred. N=67 **Conventional Clinical assessment:** Patients were managed using routine cardiovascular monitoring and	Patients requiring elective or semi-elective large bowel surgery. Median age (IQR): ODM: 69.9 years (10.2) Conventional: 69.1 years (12.3) UK	• Quality of life • Complications • Length of stay	All patients had OD but only intervention group had fluids adjusted according to ODM values.

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Study	Intervention and comparison	Population	Outcomes	Comments
	CVP measurements. The CVP was used to guide i.v. fluid administration and was kept between 12 and 15 mm Hg. N=67			
Zakhaleva 2013[108]	**Oesophageal Doppler monitoring:** Naso-oesophageal Doppler placed by anaesthesiologist. Patients received intraoperative boluses of water and electrolyte according to a predetermined algorithm which incorporated the variables of cardiac output, SV and systemic vascular resistance. N=32 **Conventional Clinical assessment:** Preoperative crystalloid loading at 2 ml/kg/h of fasting, and given infusion of crystalloid in volume of three to four times the actual blood loss. Additional crystalloid was given at 4-8ml/kg/h based on estimated insensible loss. N=40	Patients over 18 years of age presenting for bowel resection, defined as open or laparoscopic with primary anastomosis. Mean age (range): 57 years (22-80) UK	• Mortality • Complication • Length of hospital stay	

See appendix D for full evidence tables.

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1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Oesophageal Doppler monitoring versus pulse contour analysis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Pulse contour analysis	Risk difference with Oesophageal Doppler (95% CI)
Patients with complications	21 (1 study) 8 days	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 0.61 (0.34 to 1.08)	Moderate	
				900 per 1000	351 fewer per 1000 (from 594 fewer to 72 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 4: Clinical evidence summary: Cardiac output monitoring versus conventional clinical assessment

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional clinical assessment	Risk difference with Non-invasive cardiac output monitoring (95% CI)
Mortality	1915 (12 studies) <90 days	⊕⊕⊖⊖ LOW1 due to imprecision	RR 0.87 (0.53 to 1.43)	Moderate	
				34 per 1000	4 fewer per 1000 (from 16 fewer to 15 more)
Patients with complications	1853 (12 studies) <45 days	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 0.77 (0.69 to 0.87)	Moderate	
				413 per 1000	95 fewer per 1000 (from 54 fewer to 128 fewer)
Total number of complications	326 (3 studies) ≤30 days	⊕⊖⊖⊖ VERY LOW1,2 due to imprecision and inconsistency	RR 0.86 (0.56 to 1.33)	Moderate	
				441 per 1000	62 fewer per 1000 (from 194 fewer to 146 more)
Complications: POMS ≥1 (3-days)	220 (1 study) 3 days	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 1.12 (0.97 to 1.29)	Moderate	
				730 per 1000	88 more per 1000 (from 22 fewer to 212 more)
Complications: POMS ≥1 (5-days)	220 (1 study) 5 days	⊕⊕⊖⊖ LOW1 due to imprecision	RR 1.04 (0.79 to 1.35)	Moderate	
				487 per 1000	19 more per 1000

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional clinical assessment	Risk difference with Non-invasive cardiac output monitoring (95% CI)
					(from 102 fewer to 170 more)
Complications: POMS ≥1 (8-days)	220 (1 study) 8 days	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 1.27 (0.87 to 1.87)	Moderate	
				288 per 1000	78 more per 1000 (from 37 fewer to 251 more)
Length of hospital stay	941 (8 studies)	⊕⊕⊕⊕ HIGH		The mean length of hospital stay in the control groups was 12.3 days	The mean length of hospital stay in the intervention groups was 0.57 lower (1.12 to 0.03 lower)
Length of stay in ICU	214 (2 studies)	⊕⊕⊕⊕ HIGH		The mean length of stay in ICU in the control groups was 3.26 days	The mean length of stay in ICU in the intervention groups was 0.36 lower (0.59 to 0.12 lower)
Readmission rate	707 (5 studies) 30-60 days	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 1.23 (0.81 to 1.87)	Moderate	
				94 per 1000	22 more per 1000 (from 18 fewer to 82 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p=0.05, unexplained by subgroup analysis.

Table 5: Evidence not suitable for GRADE analysis: Oesophageal Doppler monitoring versus pulse contour analysis

Outcome	Study (no. of participants)	Risk of bias	Comparison results (pulse contour analysis)	Intervention results (Oesophageal Doppler)	*P* value
Length of hospital stay (days)	Feldheiser 2015 (21)	Low	Median (IQR): 13 (9.75-22.5)	Median (IQR): 13 (12-19)	0.91

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Table 6: Evidence not suitable for GRADE analysis: Cardiac output monitoring versus conventional clinical assessment

Outcome	Study (no. of participants)	Risk of bias	Comparison results (conventional clinical assessment)	Intervention results (cardiac output monitoring)	*P* value
Mortality	Moppett 2015 (114)	Low	There was no significant difference (P=0.148) with outcomes adjusted for NHFS or age. Values reported on Kaplan Meier curve		
Quality of life	Wakeling 2005 (128)	High	The EORTC QLQ C-30 and QLQ CR38 quality of life questionnaires completed 4–6 weeks after surgery showed no differences between the groups.		
Total number of complications	Pillai 2011 (66)	High	35/34	16/32	n/a
	Senagore 2009 (43)	Low	40/22	41/21	n/a
Length of hospital stay (days)	Bartha 2013 (142)	High	Median (range): 9 (3-20)	Median (range) 10 (1-38)	>0.05
	Noblett 2006 (103)	High	Median (range): 9 (4-45)	Median (range): 7 (3-35)	n/a
	Senagore 2009 (43)	Low	Mean (hours): 64.9	Mean (hours): 71.8	<0.05
	Srinivasa 2013 (85)	Low	Median (range): 5 (2-29)	Median (range): 6 (3-31)	n/a
	Stens 2017 (175)	High	Median (IQR): 6 (4-11)	Median (IQR): 6 (4-9)	n/a
	Wakeling 2005 (128)	High	Median (IQR): 11.5 (4.75)	Median (IQR): 10 (5.75)	0.031

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Outcome	Study (no. of participants)	Risk of bias	Comparison results (conventional clinical assessment)	Intervention results (cardiac output monitoring)	*P* value
	Zakhaleva 2013 (72)	Low	Median (range): 5 (3-16)	Median (range): 6 (3-30)	n/a
	Correa-Gallego 2015 (135)	Low	Median (range): 6 (5-8)	Median (range): 7 (6-8)	n/a
	Mayer 2010 (60)	Low	Median (IQR): 19 (14-23.5)	Median (IQR): 15 (12-17.75)	0.006
	Pearse 2014 (730)	Low	Median (IQR): 11 (7-17)	Median (IQR): 10 (7-14)	0.05
	Ramsingh 2013 (38)	Low	Median (IQR): 7.5 (5.25-10.75)	Median (IQR): 5 (3.75-8.25)	n/a
	Ratti 2016 (90)	Low	Median (range): 5 (3-13)	Median (range): 4 (2-10)	n/a
	Smetkin 2009 (40)	Very high	Median (IQR): 15 (13-24)	Median (IQR): 12 (8-19)	<0.05
	Shillcutt 2014 (29)	High	Median (range): 5 (1-36)	Median (range): 3 (1-10)	0.058
Length of ICU stay (hours)	Smetkin 2009 (40)	Very high	Median (IQR): 23 (21-38)	Median (IQR): 20 (18-23)	<0.05
Length of ICU stay (days)	Stens 2017 (175)	High	Median (IQR): 0 (0-0)	Median (IQR): 0 (0-0)	n/a

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See appendix F for full GRADE tables.

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1.5 Economic evidence

1.5.1 Included studies

Six health economic studies were identified with the relevant comparison and were included in this review.[5, 47, 51, 60, 63, 83] These are summarised in the health economic evidence profile below (Table 7 - Table 11) and the health economic evidence tables in appendix H.

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:.

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1.5.3 Summary of studies included in the economic evidence review

Table 7: Health economic evidence profile: Cardiac output monitoring (Cardio-Q ODM) versus pulse contour analysis (PCA) versus central venous pressure (CVP) versus conventional clinical assessment (CCA)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NICE 2011[63] (UK)	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Population: Adults undergoing moderate and major risk surgery and high risk adults undergoing any surgery • Comparators: ○ 1: CCA ○ 2: CVP & CCA ○ 3: PCA[(d)] & CCA ○ 4: CVP & ODM & CCA ○ 5: CVP & PCA[(d)] & CCA ○ 6: ODM & CCA • Cost comparison • Time horizon: until discharged from hospital	6−1: -£966[(c)] 6−2: -£1,088[(c)] 6−3: -£1,150[(c)] 6−4: -£55[(c)] 6−5: -£1,091[(c)]	None	ODM & CCA was cost-saving	Increasing the effectiveness of general ward length of stay for CVP & CCA and keeping the effectiveness of ODM constant resulted in ODM no longer being cost-saving. PSA demonstrated that ODM was cost-saving in comparison to CVP & CCA with a saving of £1,378.

Abbreviations: CCA= conventional clinical assessment; CVP= central venous pressure; ODM= oesophageal Doppler monitor; PCA= pulse contour analysis; PSA= probabilistic sensitivity analysis

(a) UK NHS perspective, costs from 2008/09 and changes in practice mean that it may not be as relevant to current practice. Measure of effect is not in line with NICE reference case methods as the analysis does not measure QALYs.

(b) Time horizon is too short and may not fully capture differences in costs and health outcomes. Some of the health benefits have not been captured and some of the treatment effects were based on assumptions. The treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review). Five out of eleven of the RCTs included in the meta-analysis used starch boluses and were excluded from the NGC clinical review. Funded by Deltex Medical.

(c) 2008/09 UK Pounds. Cost components included: Length of hospital stay (ICU, HDU and general ward), device costs, maintenance and consumables, fluids and staffing.

(d) Note: Pulse contour analysis was used as the name of the intervention throughout the review instead of pulse pressure waveform analysis to be in line with the clinical review.

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Table 8: Health economic evidence profile: Cardiac output monitoring (LiDCO plus) versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Bartha 2012 (Sweden)[5]	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Population: Adults 80 years and over undergoing surgery for hip fractures • Comparators: ○ Standard care ○ Cardiac output-monitoring (LiDCO rapid) • Cost utility analysis • Probabilistic decision analytic model • Time horizon: 5 years	-£1,436[(c)]	**QALYs:** 0.344	Cardiac output monitoring was dominant[(d)] (cheaper and more effective)	96.4% of simulations resulted in cardiac output monitoring being dominant. Results were sensitive to relative risks for mortality and morbidity. When clinical effect was reduced by increasing the relative risk by 90% the ICER was £292 per QALY gained.
Sadique 2015[83] (UK)	Partially applicable[(e)]	Potentially serious limitations[(f)]	• Population: Adults 50 years and over undergoing major gastrointestinal surgery • Comparators: ○ Standard care ○ Cardiac output monitoring (LiDCO rapid) • Cost utility analysis • Within trial analysis (RCT) with modelled post-trial extrapolation • Time horizon: 10 years	**Lifetime:** **-**£404[(g)] **Six months:** -£404[(g)]	**Lifetime QALYs:** 0.19 **Six month QALYs:** 0.01	Cardiac output monitoring was dominant[(d)] (cheaper and more effective)	Different scenario analyses were conducted, which did not affect the results.

Abbreviations: QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) Swedish healthcare perspective and 2012 Swedish kroners may not be relevant to current UK practice. Study focuses on one type of surgery instead of all major surgery. Unclear what tariff and population was used for quality of life weights, cost year is not reported and discount rate used is not in line with NICE reference case.

(b) Time horizon may be too short to fully capture costs and outcomes. Baseline probabilities and treatment effects for complications were based on a single RCT therefore the treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review).

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(c) 2012 Swedish Kroner covered to UK pounds. [68] Cost components included: monitor costs (LiDCO rapid), hospital costs, costs of various complications in hospital, costs of long-term medical care costs after stroke and cardiovascular complications and death.

(d) Interventions are dominant when they are both less costly and more effective.
(e) UK NHS perspective and costs from 2012/13 may not reflect current practice. Study is based on one type of surgery and not the whole surgical population. Unclear if costs are discounted.
(f) Baseline and treatment effects are based on a single RCT therefore the treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review). The analysis did not include complications as a health outcome. Cost source slightly unclear and costing methods to avoid double counting could impact results.
(g) 2012/13 UK Pounds. Cost components included: surgical costs, length of stay in critical care and surgical ward, blood products and device costs.

Table 9: Health economic evidence profile: ODM & CCA versus PCA & CCA versus CCA

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Legrand 2015[47] (France)	Partially applicable (a)	Potentially serious limitations (b)	• Population: Adults undergoing intermediate and high risk abdominal surgery. • Comparators: ○ 1: CCA alone ○ 2: PCA(d) & CCA ○ 3: ODM & CCA • Cost-effectiveness analysis • Time horizon: until discharged from hospital	2−1: -£334(c) 3-1: -£134(c) 3-2: £200(c)	**Major complication avoided:** 2−1: 0.129 3−1: 0.072 3−2: -0.057 **Death avoided:** 2−1: 0.018 3−1: 0.021 3−2: 0.003	Both PCA and ODM were dominant(e) when they were compared to CCA.	One-way sensitivity analysis was conducted varying each of the parameters. Probabilistic sensitivity analysis was conducted by performing 1000 iterations. For mortality avoided PPWA and ODM were dominant compared with CCA in 92.9% and 69.5% of cases, respectively. For major complications avoided PPWA and ODM were dominant compared with CCA in 97.3% and 76.1% of cases, respectively.

Abbreviations: CCA= conventional clinical assessment; ODM= oesophageal Doppler monitor, PCA= pulse contour analysis
(a) French healthcare perspective and 2011 euros may not be relevant to current UK practice. Study focuses on one type of surgery and does not include all major surgery. Measure of effect is not in line with NICE reference case methods as the analysis does not measure QALYs.
(b) Time horizon may be too short to fully capture costs and outcomes. The treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review). Five out of thirteen of the RCTs included in the meta-analysis used starch boluses and were excluded from the NGC clinical review.

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(c) 2011 French Euros covered to UK pounds.[68]. Cost components included: Medical devices (CardioQ-ODM and Vigileo/FloTrac), hospital costs such as procedures performed, length of stay and complications.

(d) Note: Pulse contour analysis was used as the name of the intervention throughout the review instead of pulse pressure waveform analysis to be in line with the clinical review.

(e) *Interventions are dominant when they are both less costly and more effective.*

Table 10: Health economic evidence profile: CCA & CVP & ODM versus CCA & CVP versus ODM & CCA versus CCA

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Maeso 2011[51] (Spain)	Partially applicable[(a)]	Potentially serious limitations [(b)]	• Population: Adults undergoing colorectal resection. • Comparators: ○ 1: CCA ○ 2: ODM & CCA ○ 3: CCA & CVP ○ 4: CCA & CVP & ODM • Cost-effectiveness analysis and cost-utility analysis • Time horizon: for the CEA until discharged, and for the CUA a lifetime horizon	**Costs until discharged (mean per patient):** 4−1: -£931[(c)] 4−2: -£364[(c)] 4−3: -£882[(c)] **Costs for lifetime horizon (mean per patient):** 4−1: -£402[(c)] 4−2: £154[(c)] 4−3: -£803[(c)]	**Survival rate (mean per patient):** 4−1: 0.093 4−2: 0.091 4−3: 0.014 **Free of major complication rate (mean per patient):** 4−1: 0.232 4−2: 0.152 4−3: 0.115 **QALYs (mean per patient):** 4−1: 1.37 4−2: 1.34 4−3: 0.21	**CEA:** CCA & CVP & ODM was dominant[(d)] for survival and major complication avoided compared to other interventions. **CUA:** CCA & CVP & ODM dominated CCA and CVP and CCA alone. Compared against CCA & ODM it resulted in an ICER of £114.93 per QALY.	Deterministic sensitivity analyses were performed by varying uncertain parameter values. Probabilistic sensitivity analysis was conducted by performing 10,000 iterations. The probability of CCA & CVP & ODM being cost-effective ranged from 40% to 60% at €50,000 per death avoided.

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Abbreviations: CCA= conventional clinical assessment; CVP= central venous pressure; ICER= incremental cost-effectiveness ratio; ODM= oesophageal Doppler monitor; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) Spanish healthcare perspective and 2007 euros may not be relevant to current UK practice. Study focuses on one type of surgery instead of all major surgery. QALYs were only included in a sensitivity analysis.

(b) Time horizon of until discharge was too short to fully capture outcomes and costs. Did conduct a sensitivity analysis with long-term horizon but assumed that people alive would incur the same costs and QALYs. The treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review) and some of the treatment effects were obtained from other high risk surgeries where there was missing data for certain comparisons. One out of four of the RCTs included in the meta-analysis used starch boluses and was excluded from the NGC clinical review.

(c) 2007 Spanish Euros covered to UK pounds.[68]. Cost components included: Device costs, surgery time, hospital stay and high dependency unit stay. Staff costs were assumed to be included in the surgery time cost.

(d) *Interventions are dominant when they are both less costly and more effective.*

Table 11: Health economic evidence profile: ODM & CCA versus CCA and CCA & CVP & ODM versus CVP & CCA

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Mowatt 2009[60] (UK)	Partially applicable[(a)]	Potentially serious limitations [(b)]	• Population: Adults undergoing high risk surgery • Comparisons: ○ ODM & CCA versus CCA ○ CCA & CVP & ODM versus CVP & CCA • Cost-utility analysis • Time horizon: 5 years	NR	NR	Study concluded that both ODM strategies are cost-effective at a threshold of £30,000 per QALY.	Probabilistic sensitivity analysis was conducted by performing 1000 iterations. The probability of ODM being cost-effective was not reported however most of the iterations fell in the south-east quadrant for both of the ODM & CVP & CCA versus CVP & CCA and ODM & CCA versus CCA comparisons, meaning ODM was more effective and less costly.

Abbreviations: CCA= conventional clinical assessment; CVP= central venous pressure; ODM= oesophageal Doppler monitor; QALY= quality-adjusted life years;

(a) UK NHS perspective, costs from 2006/07 and changes in practice mean that it may not be relevant to current practice. Did not state whether discounting was used in 5 year analysis. Utilities were not from the relevant population as it was obtained from ICU survivors instead of surgery survivors.

(b) Does not give a breakdown of the costs for each interventions and a breakdown of the QALYs for each intervention. Shows the probability that ODM would be considered cost-effective at a £30,000 per QALY threshold, not £20,000. Assumes that people survive on average for 5 years after surgery. The treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review). Five out of nine of the RCTs included in the meta-analysis used starch boluses and were excluded from the NGC clinical review.

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1.5.4 Health economic modelling

Model methods

A previous NICE medical technologies guidance (MTG3) assessed the clinical and cost-effectiveness of the CardioQ-ODM oesophageal Doppler monitor and recommended to consider the use of monitoring in people undergoing high risk or major surgery. Since the publication of this medical technology guidance in 2011, there have been improvements in the perioperative care pathway, which have resulted in reductions in complications and length of stay. Although six published economic analyses were assessed and included in the review, methodological limitations meant there was still uncertainty about cost effectiveness. Additionally, variation in current practice and improvements in perioperative care and outcomes since MTG3 meant that the savings in MTG3 might not be as significant as previously demonstrated. For these reasons, alongside the fact that the monitors have a high cost, this area was prioritised for original economic analysis.

A cost-utility analysis was undertaken with lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance. An incremental analysis was undertaken.

The population was adults having major or complex or high risk surgery and high risk adults undergoing any surgery. Due to this population typically having worse health than the general population, using general population data such as mortality for the baseline data wasn't felt appropriate. The committee agreed that that a large proportion of major surgery in England is for treating people with cancer, and some of the studies included in the clinical review were for adults undergoing major bowel or gastrointestinal surgery therefore adults with bowel cancer was chosen as the base case population.

The first part of the model consisted of a 30-day decision tree which modelled the probability of experiencing complications or death up to 30 days post-surgery, with these probabilities being taken from the clinical review. This found that COM reduced complications and also led to small reduction in mortality. Those that experienced complications were further broken down in to those having minor (Clavien-Dindo grades 1 and 2) and major (Clavien-Dindo grades 3 and 4) complications. The decision tree applied a different cost and utility to those that experienced complications. For minor complications, a quality of life decrement associated with a chest infection was applied and the NHS reference costs associated with a chest infection was also applied as a one off cost. For those experiencing major complications, the NHS reference costs and quality of life associated with being admitted to ICU was applied. Those that did not experience complications did not have any costs applied in the decision tree and the quality of life associated with bowel cancer was applied.

The second part of the model was a Markov model to capture costs and outcomes over a lifetime. A one year cycle length was used. Adults alive at the end of 30 days entered the Markov model. The Markov model was made up of 3 health states: 'alive with no complications', 'alive with complications' and 'dead'. People that experienced major complications in the decision tree entered the 'alive with complications' health state, as it was agreed that they would experience long-term health implications which resulted in higher mortality and lower quality of life, compared to those alive with no complications. Those with minor complications entered the 'Alive with no complications' health state as it was assumed that their minor complication would be dealt with within 30 days. Those who experienced no complications in the decision tree also entered the 'Alive with no complications' health state. The probability of transitioning to the dead health state was based on bowel cancer related mortality rates. Those in the 'alive with complications' health state had a higher probability of death for the first 3 years, at which point it returned to the baseline. This was based on a cohort study conducted in England which showed people experiencing complications 15

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days after surgery had a higher probability of death for 3 years, and then it returns to baseline.[58] The committee highlighted that once a person has been cancer free for over eight years, their mortality returns to that of the general population. Therefore, bowel cancer mortality rates were applied for 10 years. The bowel cancer mortality data supported this as it showed that at 10 years there was no change in net excess mortality. General population mortality was then applied for the following years until the end of the time horizon. The quality of life associated with having bowel cancer was applied for 10 years in the model, and then it returned to the age-related general population quality of life. Costs associated with living with bowel cancer were also applied for 9 years and were obtained from a study conducted in England.[44] Those in the 'alive with complications' health state had quality of life associated with ICU survivors applied for 3 years as well as additional costs associated with ICU survivors taken from a study conducted in Scotland.[49]

Results

The base case results showed that cardiac output monitoring was associated with additional costs and higher QALYs with an ICER of £377 per QALY gained, which is considered cost-effective at the NICE threshold of £20,000 per QALY gained. Table 12 shows the 30 day and lifetime results.

Table 12: Probabilistic base case results (per person)

	Total cost	Total QALYs	ICER	Probability COM CE at £20k
30 day results				
CCA	£1,177	0.050		
COM	£1,033	0.051		
Incremental (COM vs CCA)	-£144	0.001	COM dominant[(a)]	n/a
Lifetime results (discounted)				
CCA	£27,748	7.07		
COM	£27,768	7.14		
Incremental (COM vs CCA)	**£20**	**0.07**	**£285**	**97%**

Abbreviations: CE = cost-effective; ICER = incremental cost-effectiveness ratio; n/a = not applicable; QALYs = quality-adjusted life years

(a) Interventions are dominant when they are both less costly and more effective.

Various sensitivity analyses were conducted to test to the robustness of results. Firstly, different treatment effects were used and showed that COM remained cost-effective or was dominant when: excluding non-UK studies; excluding cardiac and emergency surgery; and excluding studies that were conducted before the publication of MTG3. Other sensitivity analyses were conducted to make inputs conservative towards COM, and in all analyses COM remained cost-effective. In one analysis, the ICER increased to above £16,000, and this was where: pre-MTG3 studies were excluded from the treatment effects; assuming there was no 30 day mortality difference; and using the upper confidence interval value for complications treatment effect (which was very close to 1). Sensitivity analyses showed that the model was sensitive to the treatment effects and the mortality rates used in the Markov model. For example, when using the general population mortality rates instead of the bowel cancer mortality rates, there was a smaller QALY difference between the two comparators. Also, some of the costs used in the model had some impact on results, such as removing the cancer related costs. This resulted in COM being dominant, as when cancer costs are included then more people are alive in the COM arm to accrue expensive healthcare costs from cancer, making the COM arm more expensive, and therefore omitting these made COM cheaper compared to CCA.

Limitations of the model included the use of the proxy bowel cancer population. Although the committee agreed that this was more representative of the major surgical population, it could

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have overestimated the mortality in the model. This was tested in a sensitivity analysis by using general population mortality rates and this did not impact conclusions. Treatment effects were based on the guideline clinical review, and the committee highlighted some issues with this data. Firstly, there were only a small number of studies published since MTG3, which was a limitation as current practice has evolved since 2011 and since a lot of the included studies were conducted. Some of the randomised controlled trials would have included central venous pressure as part of conventional clinical assessment, which is no longer considered standard practice. Also, there has been a trend towards administering fewer fluids in recent years. Another limitation involved the assumptions made regarding complications. The data used in the model to represent a minor complication was based on a chest infection. This was very specific, and in reality people can experience many different types of minor complications. Also, the assumption that a minor complication would not impact health after 30 days could vary in real life, however the committee highlighted that there was no available evidence to indicate how long the impact would last. In addition, major complications were associated with a long-term cost and health impact of 3 years. Although this was based on published evidence, the committee highlighted that this could vary between different types of surgery and different people.

1.6 Evidence statements

1.6.1 Clinical evidence statements

Oesophageal Doppler monitoring versus pulse contour analysis

Complications

One study showed a clinically important benefit of Oesophageal Doppler monitoring for the number of patients experiencing complications at 8 days compared to pulse contour analysis (1 study, n=21, moderate quality evidence).

Evidence not suitable for GRADE analysis

One study showed no statistically significant difference in length of hospital stay between Oesophageal Doppler monitoring and pulse contour analysis (1 study, n=21, low risk of bias)

Cardiac output monitoring versus conventional clinical assessment

Mortality

Twelve studies demonstrated no clinically important difference in mortality between cardiac output monitoring and conventional clinical assessment (12 studies, n=1915, low quality evidence).

Complications

Twelve studies found a clinical benefit of cardiac output monitoring for the number of patients with complications compared to conventional clinical assessment (12 studies, n=1853, moderate quality evidence).

Five studies showed a clinical benefit of cardiac output monitoring for the number of complications compared to conventional clinical assessment (5 studies, n=435, moderate quality evidence).

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One study found no clinical difference in complications (POMS ≥1) at 3-days between cardiac output monitoring and conventional clinical assessment (1 study, n=220, moderate quality evidence).

One study found no clinical difference in complications (POMS ≥1) at 5-days between cardiac output monitoring and conventional clinical assessment (1 study, n=220, low quality evidence).

One study found no clinical difference in complications (POMS ≥1) at 8-days between cardiac output monitoring and conventional clinical assessment (1 study, n=220, moderate quality evidence).

Length of hospital stay

Eight studies showed no clinically important difference for length of hospital stay between cardiac output monitoring and conventional clinical assessment (8 studies, n=941, high quality evidence).

Length of ICU stay

Two studies found no clinically important difference in length of stay in ICU between cardiac output monitoring and conventional clinical assessment (2 studies, n=214, high quality evidence).

Readmission

Five studies showed no clinically important difference in readmission rate between cardiac output monitoring and conventional clinical assessment (5 studies, n=707, moderate quality evidence).

Evidence not suitable for GRADE analysis

One study found no statistically difference in mortality between cardiac output monitoring and conventional clinical assessment (1 study, n=114, low risk of bias).

One study found no notable difference in quality of life at 4-6 weeks between cardiac output monitoring and conventional clinical assessment (1 study, n=128, high risk of bias).

Two studies showed a a trend to benefit with cardiac output monitoring for total number of complications compared to conventional clinical assessment (2 studies, n=109, high risk of bias)

Fifteen studies showed no statistically significant difference in length of hospital stay between cardiac output monitoring and conventional clinical assessment (15 studies, n=2044, high risk of bias).

One study showed no statistically significant difference in length of ICU stay (days) between cardiac output monitoring and conventional clinical assessment (1 study, n=175, high risk of bias).

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One study showed a statistically significant benefit with cardiac output monitoring in length of ICU stay (hours) compared to conventional clinical assessment (1 study, n=40, very high risk of bias).

1.6.2 Health economic evidence statements

- One original cost–utility analysis found that COM was cost effective compared to CCA in adults having major or complex or high risk surgery and high risk adults undergoing any surgery (ICER: £286 per QALY gained). This analysis was assessed as directly applicable with minor limitations.
- One cost–utility analysis found that in adults 50 years and over undergoing major gastrointestinal surgery cardiac output monitoring was dominant (less costly and more effective) compared to conventional clinical assessment. This analysis was assessed as partially applicable with potentially serious limitations.
- One comparative cost analysis found that oesophageal Doppler monitoring was cost saving compared to conventional clinical assessment in adults undergoing moderate and major risk surgery and high risk adults undergoing any surgery (cost difference: £1,091 per patient). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that in adults 80 years and over undergoing surgery for hip fractures COM was dominant (less costly and more effective) compared to standard care. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-effectiveness analysis found that in adults undergoing intermediate and high risk abdominal surgery cardiac output monitoring (ODM and PCA) was dominant (less costly and more effective) compared to CCA. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-effectiveness and cost-utility analysis found that in adults undergoing colorectal resection cardiac output monitoring (ODM with CCA and CVP) was dominant (less costly and more effective) compared to CCA. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that [in adults undergoing high risk surgery ODM was cost-effective at a threshold of £30,000 compared to CCA. This analysis was assessed as partially applicable with potentially serious limitations.

1.7 The committee's discussion of the evidence

Please see recommendation 1.4.5 in the guideline.

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee agreed that cardiac output monitoring is primarily used within perioperative practice to achieve fluid optimisation and guide the use of vasoactive and inotropic drugs with the goal of reducing the metabolic impact of surgery on patients undergoing major surgery. As such, the committee considered health related quality of life, mortality and perioperative complications as critical outcomes to decision making. Length of hospital stay,

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length of stay in the intensive care unit and hospital readmission were also considered to be important outcomes.

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 moderate quality. This was mostly due to imprecision of data. The committee felt that the evidence was of sufficient quality and quantity to support the recommendations made.

Outcomes which were not suitable for GRADE analysis were considered to be at low and high risk of bias.

1.7.1.3 Benefits and harms

The committee discussed the evidence on cardiac output monitoring in adults having major or complex or high risk surgery and high risk patients undergoing any surgery.

The committee noted evidence from one small study with 21 participants showing a benefit of fewer complications with Oesophageal Doppler monitoring when compared to pulse contour analysis. This study also showed no clinical difference in length of stay. The committee agreed that this evidence was insufficient to support any recommendation.

In a comparison of cardiac output monitors to conventional clinical assessment, the committee agreed that there was no clear benefit of one type of monitor over another. As such, interventions of COM were grouped for an overall comparison with conventional clinical assessment. From this dataset, the committee agreed that there was a benefit of COM with fewer total complications compared to conventional care. The committee also noted a trend towards a benefit for length of stay with COM, but highlighted a variation in results due possibly to the heterogeneity in populations included in the analysis. The committee discussed a possible harm of COM for readmissions but noted the low quality of evidence caused by serious imprecision. The committee considered the possibility of increased readmissions with COM being linked to a shorter length of stay with the intervention. No difference was found between COM and conventional care in mortality. The committee considered that the noted benefits in a reduced complication rate and shorter length of stay were significant and on balance with low quality evidence of increased readmission rates demonstrated an overall positive effect with the use of COM.

1.7.2 Cost effectiveness and resource use

Six published economic studies were included that compared cardiac output monitoring to conventional clinical assessment. Three of these were from a UK NHS perspective. One of the three being the manufacturer submission for the NICE medical technologies guidance 3 (MTG3), on CardioQ-ODM. This was a cost-comparison that involved six strategies, comparing oesophageal Doppler monitoring (ODM) in addition to conventional clinical assessment (CCA) with: CCA alone, central venous pressure (CVP) + CCA, pulse pressure waveform analysis (PPWA) + CCA, CVP + ODM + CCA, and CVP + PPWA + CCA. The analysis showed that ODM with CCA was cost-saving when compared to all other interventions. This study was rated as partially applicable with potentially serious limitations. This was for reasons such as not having any health outcomes. Some of the RCTs included in the analysis were excluded from clinical review due to starch boluses being used, and the time horizon was only ‘in-hospital stay’ thereby potentially omitting any long-term impact on costs and quality of life. The cost savings were largely attributable to the length of hospital stay savings associated with ODM. The analysis assumed that CardioQ-ODM was associated with a reduction in length of stay of 1.92 days, which was based on a combination of randomised controlled trials and audit data. The committee highlighted issues with this

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assumption as length of hospital stay data from randomised controlled trials can vary based on the country they are conducted in, and are not always reflective of current UK practice.

The second UK analysis was a cost-utility analysis for high risk surgical adults and compared ODM + CCA to CCA alone, as well as a second comparison which added CVP to both arms. A meta-analysis was conducted and the outcomes that fed in to the model were mortality and length of stay. This study did not give a breakdown of the costs or QALYs for each intervention but concluded that ODM was cost-effective at a threshold of £30,000 per QALY. No results were presented for a threshold of £20,000 per QALY. This study was rated as partially applicable with potentially serious limitations, as some of the RCTs included used starch boluses and the assumption that adults would only survive an average of five years post-surgery was not considered a reflection of what happens after surgery.

The third UK analysis was a cost-utility analysis with a lifetime horizon based on a single RCT (OPTIMISE), which is included in the clinical review. This study looked at pulse contour analysis (PCA) versus CCA in adults undergoing major gastrointestinal surgery. This analysis found that PCA was dominant. Results at six months were reported as well as lifetime results, and the intervention was dominant in both scenarios. Cost-savings were based on the reduction in hospital length of stay that was seen in the trial. The committee felt that as this was a UK study, the length of stay data was more reliable. However, limitations included: it only looked at one type of surgery and not the whole surgical population, it was based on a single RCT, standard care involved central venous pressure in some cases, cost sources were unclear and costing methods to avoid double counting may have impacted results. This study was given an overall rating of partially applicable with potentially serious limitations.

One study conducted a cost-effectiveness analysis from a French healthcare perspective on adults undergoing intermediate and high risk abdominal surgery. The study compared ODM + CCA, PCA + CCA and CCA alone. A meta-analysis was conducted which identified 13 RCTs and the model incorporated death and major complications. The study found that both types of cardiac output monitoring were dominant when compared to CCA, in terms of being less costly and reducing the number of complications and death. This study was rated as partially applicable with potentially serious limitations due to it being non-UK and only looking at abdominal surgery. Also, the time horizon was until hospital discharge which is too short to fully capture costs and outcomes and some of the RCTs included in the analysis used starch boluses.

One study from a Spanish healthcare perspective conducted a cost-effectiveness analysis for adults undergoing colorectal resection. They also conducted a cost-utility analysis as part of a sensitivity analysis. ODM +CCA was compared to CCA alone. Another analysis looked at adding CVP to both arms. Treatment effects were obtained from a meta-analysis of three RCTs. The study concluded that ODM increased health benefits (in terms of survival rate and reduction in complications) and reduced costs, which made it dominant. This study was rated as partially applicable with potentially serious limitations. Reasons for this rating included the Spanish healthcare perspective; the analysis only looked at one type of surgery and used treatment effects from other types of surgery to inform the analysis. Also, one of the RCTs included starch boluses and the analysis incorporated length of hospital stay from one RCT which was conducted in 2005 and may not be relevant to current practice.

The final analysis was a cost utility analysis from a Swedish healthcare perspective, that looked at COM compared to CCA in adults over 80 years old undergoing surgery for a hip fracture. A five-year time horizon was used to model longer term impacts of complications such as cardiac complications and stroke. Cardiac output monitoring resulted in less costs and additional QALYs over the five-year time horizon. The committee agreed that in emergency surgery cardiac output monitoring may be used more and is probably more likely to be cost-effective as the adult undergoing surgery may already be at a higher risk than someone undergoing elective surgery. This study was rated as partially applicable with

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potentially serious limitations. Reasons for this rating included the Swedish healthcare perspective may not be relevant to current UK practice, the analysis focuses on one type of surgery and it is unclear what tariff and population was used to obtained quality of life weights. Also, treatment effects were obtained from various studies looking at cardiac output monitoring that were not directly relevant to the surgery and population in the analysis.

After reviewing the published evidence, the committee considered there to still be uncertainty about the cost effectiveness of cardiac output monitoring versus conventional assessment in the current NHS setting, and prioritised this area for new analysis. Reasons for this uncertainty included: the studies relevant to the UK NHS were out of date or based on only a few studies for treatment effect. On a related point, committee opinion was that CCA has improved in the last decade, and therefore the relative cardiac output monitoring benefits may not be as large compared to previously, therefore the committee agreed there was likely to be new clinical data capturing this that could be used in a model. CCA improvement is based on a number of reasons such as central venous pressure no longer being used in current practice. Additionally, certain surgical techniques have also improved, for example the use of laparoscopic surgery instead of open surgery. The introduction of enhanced recovery programmes also means there are many processes as part of the surgical pathway which have reduced overall complications and length of stay. Also, some of the published evidence was in a specific population or only looked at one type of monitor, and the committee agreed that it was useful to analyse all of the data together for all surgeries and all monitors combined, and use this more up to date pooled data in a model, to see if COM was still considered cost effective.

A decision analytic model was constructed to compare COM to CCA. The committee highlighted that the population being modelled would be higher risk than the general population, therefore bowel cancer was chosen as a proxy population. The model structure consisted of a 30-day decision tree capturing the hospital period, followed by a lifetime Markov model with one year cycles. Treatment effects were taken from the clinical review to inform the decision tree, which had branches of death, complications, and no complications. Complications were broken up into minor and major complications. Intervention costs were based on a weighted average of the costs of the most commonly used monitors. No costs were attributed to the CCA arm, as the only difference in costs would be use of the monitor. After 30 days people that were alive entered a three-state Markov cohort model. The health states were death, alive without complications, and alive with complications. Those that experienced no or minor complications in the decision tree both entered the ‘alive without complications’ state. Those that experienced major complications were assumed to have long term health implications and entered the ‘alive with complications’ state. Mortality associated with bowel cancer was added to the general population mortality and the cancer mortality only applied for 10 years. Costs and quality of life associated with having bowel cancer were applied in the model. For those that experienced major complications, hazard ratios were applied to the mortality rate for three years post-operatively and they had additional costs and lower quality of life associated with ICU survivors applied for three years.

Results showed that the upfront cost of cardiac output monitoring was offset in the short term by the reduction in complications, as the 30-day results showed that COM was dominant. The lifetime results showed an ICER of £285 per QALY when comparing COM to CCA. Various sensitivity analyses were conducted to test the robustness of the results. Treatment effects were tested by: excluding trials that were not conducted in the UK, excluding trials in cardiac and emergency surgery , and excluding studies that were conducted before the publication of MTG3 (2011) – this left 6 studies. All showed COM to be dominant. Various sensitivity analyses were also conducted which assumed no 30-day mortality in the decision tree, as the committee did not believe that the type of haemodynamic monitoring would impact mortality. All of these analyses did not impact conclusions, however the ICER increased to £16,881 when the complications treatment effect was changed to the upper confidence interval value for studies conducted after the publication of MTG3.

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Various other inputs were varied such as the cost of complications, the cost of the interventions, and inputs related to the population such as assuming the population was the general population (and using general population mortality and no cancer costs). Age-specific costs were also incorporated in another analysis. Some sensitivity analyses varied various inputs to make the analyses conservative to COM to see if it would still be cost effective (for example, making adverse events cheaper alongside using the upper confidence interval of the relative risk of complications). In all these analyses COM remained cost effective with ICERs below £20,000 per QALY gained.

Limitations of the model included the assumptions about the base case population. As the population of interest was very broad, a proxy population of bowel cancer was chosen for the base case analysis. However, not everyone having major or complex surgery would be undergoing surgery for cancer. Also, the data that was used to inform the cancer mortality was taken from all adults diagnosed with bowel cancer in England and Wales and not everyone would have undergone surgery. There were also assumptions made regarding the type of complications in the model which can vary greatly between adults and different types of surgery. In addition, it was assumed that minor complications did not have any long-term impact on health but this could also vary. The committee agreed that although some minor complications could have long-term impacts, there was no evidence to support this. Extensive sensitivity analysis was undertaken and the conclusion was considered robust.

The committee discussed the clinical evidence and agreed that there was a signal of clinical effectiveness of COM with regards to avoiding complications in particular when complications were combined. The committee agreed that there were uncertainties in the clinical evidence used to inform the model, as there had been a limited number of studies published since MTG3 and there was uncertainty around mortality. Although their interpretation of the model was that the conclusions were robust in favour of COM, even when considering only complications and not mortality. The model was robust to inputs varying in sensitivity analyses. They discussed the many improvements that had been made in CCA since the recommendation from the NICE medical technologies' guidance, such as the introduction of enhanced recovery programmes and a general trend towards administering less intravenous fluids, which led to the committee feeling that although there was evidence of effectiveness from the review, they were not entirely convinced that there would be additional benefit from COM. They agreed that clinical judgement was an important indicator as the adult's health state and type of surgery can determine whether or not to use cardiac output monitoring. As a result, the committee agreed to recommend that cardiac output monitoring should be considered for use during major complex or high-risk surgery. This would give flexibility to clinicians who are already using COM, but also to those who are not. It would allow consideration about whether COM could be beneficial to specific cases.

The committee discussed that recommending cardiac output monitoring would not lead to a significant change in practice as most hospitals already have some cardiac output monitoring machines. The committee indicated that since the publication of MTG3 the uptake of cardiac output monitoring was significant especially for the use of the oesophageal Doppler monitor. Despite the large uptake of the machines, there is variation in practice as some anaesthetists may use the machines more than others.

1.7.3 Other factors the committee took into account

The committee noted that as surgical techniques have developed so have approaches to fluid management. As such, the observed benefit of cardiac output monitoring may be lessened in contemporaneous medicine. The committee added that central venous pressure monitoring is no longer used in contemporaneous clinical practice to evaluate patient fluid status, and may contribute towards improved conventional clinical assessment.

The committee noted that for laparoscopic and less complex surgery, COM is not standard in current practice, but is more common and more likely to demonstrate benefit for complex, emergency and tertiary patients.

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The committee agreed that COM is now generally used as part of multimodal patient monitoring and therefore assists as a component in informing decisions about intravenous fluid requirements. COM is however less likely to be used as a singularly didactic indicator for the administration of intravenous fluids. The committee appreciated the body of evidence on goal directed fluid therapy and the contemporaneous move towards less liberal intravenous fluid administration perioperatively in general. The consensus was that current practice is more bespoke when considering monitoring for complex, emergency and tertiary patients and might include COM in such situations.

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Appendices

Appendix A: Review protocols

Table 13: Review protocol: Cardiac output monitoring

ID	Field	Content
0.	PROSPERO registration number	Not registered on PROSPERO
1.	Review title	What is the clinical and cost effectiveness of non-invasive cardiac output monitoring during major, complex or high risk surgery in adults?
2.	Review question	What is the clinical and cost effectiveness of non-invasive cardiac output monitoring during major, complex or high risk surgery in adults?
3.	Objective	To determine the clinical and cost effectiveness of non-invasive cardiac output monitoring during surgery in adults.
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 major or complex or high risk surgery (based on NICE preoperative tests for elective surgery guideline categorisation) and high risk patients (based on American Society of Anesthesiologists physical status grade) undergoing any surgery. Exclusion: • children and young people aged 17 years and younger • surgery for burns, traumatic brain injury or neurosurgery • interventions including starch bolus
7.	Intervention/Exposure/Test	• non-invasive cardiac output monitoring

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		○ oesophageal doppler monitor ○ trans-oesophageal echocardiography ○ thoracic electrical bioimpedance ○ pulse pressure waveform analysis ○ systems based on pulse contour analysis and dye dilution
8.	Comparator/Reference standard/Confounding factors	• pulmonary artery catheter • conventional clinical assessment
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 • perioperative complications 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 • length of stay in intensive care unit • hospital readmission 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

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		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.

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		• 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 (>60 years)
		• American Society of Anesthesiologists (ASA) Physical Status grade (in adults having major/complex surgery)
		• surgery grade based on NICE preoperative tests for elective surgery guideline categorisation (for high-risk adults undergoing any surgery)
		• Method of intervention (for comparison to conventional care)
		  ○ oesophageal doppler monitor
		  ○ trans-oesophageal echocardiography
		  ○ thoracic electrical bioimpedance
		  ○ pulse pressure waveform analysis
		  ○ systems based on pulse contour analysis and dye dilution	

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.]	

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<table>
<tr><td rowspan="8">23.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

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5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) and the National Guideline Centre</td></tr>
<tr><td>25.</td><td>Review team members</td><td colspan="3">From the National Guideline Centre:
Ms Kate Ashmore
Ms Kate Kelley
Ms Sharon Swaine
Mr Ben Mayer
Ms Maria Smyth
Mr Vimal Bedia
Mr Audrius Stonkus
Ms Madelaine Zucker
Ms Margaret Constanti
Ms Annabelle Davis
Ms Lina Gulhane</td></tr>
<tr><td>26.</td><td>Funding sources/sponsor</td><td colspan="3">This systematic review is being completed by the National Guideline Centre which receives funding from NICE.</td></tr>
<tr><td>27.</td><td>Conflicts of interest</td><td colspan="3">All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert</td></tr>
</table>

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		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.	
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, cardiac monitoring	
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	Commissioning information: Update MTG3 Cardiac monitoring devices as part of this new guideline. The guidance review found that significant changes in the care pathway involving CardioQ-ODM meant there	

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		was a case for updating the guidance from both clinical and economic perspectives. Since MTG3 was published, system-wide initiatives to improve perioperative care, such as the Enhanced Recovery Programmes, may have resulted in interventions, (including intraoperative fluid management (IOFM) using technologies such as CardioQ-ODM), becoming widely adopted for major surgery.
36.	Details of final publication	www.nice.org.uk

1

2 **Table 14: 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).[62] **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

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	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,

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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.[62]

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 15: 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/ or exp Monitoring, Intraoperative/
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/

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14.	case report/
15.	Intraoperative Care/ or exp Intraoperative Period/ or exp Perioperative Nursing/ or exp Monitoring, Intraoperative/
16.	((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.
17.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 during adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	or/1-3
19.	limit 4 to English language
20.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
21.	5 not 6
22.	letter/
23.	editorial/
24.	news/
25.	exp historical article/
26.	Anecdotes as Topic/
27.	comment/
28.	case report/
29.	(letter or comment*).ti.
30.	or/8-15
31.	randomized controlled trial/ or random*.ti,ab.
32.	16 not 17
33.	animals/ not humans/
34.	exp Animals, Laboratory/
35.	exp Animal Experimentation/
36.	exp Models, Animal/
37.	exp Rodentia/
38.	(rat or rats or mouse or mice).ti.
39.	or/18-24
40.	7 not 25
41.	exp Echocardiography/
42.	Cardiography, Impedance/
43.	((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 (echocardiogra* or doppler)).ti,ab.
44.	TEE.ti,ab.
45.	Plethysmography, Impedance/
46.	((bioimpedance* or impedance*) adj (cardiograp* or plethysmogra* or phlebogra*)).ti,ab.
47.	((thoracic or transthoracic) adj electric* bioimpedance*).ti,ab.
48.	Pulse Wave Analysis/
49.	((pulse* or arterial) adj3 (contour or power or wave*)).ti,ab.
50.	Dye Dilution Technique/
51.	((dye or indicator or lithium) adj3 dilut*).ti,ab.
52.	(electric* adj (cardiometry or velocimetry)).ti,ab.
53.	Pressure recording analy*.ti,ab.

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54.	bioreactance*.ti,ab.
55.	Hemodynamic Monitoring/
56.	(h?emodynamic adj3 (output* or index or monitor* or measur* or record* or reading* or track* or assess*)).ti,ab.
57.	exp Cardiac Output/
58.	(cardiac adj3 (output* or index or monitor* or measur* or record* or reading* or track* or assess*)).ti,ab.
59.	or/27-44
60.	26 and 45
61.	randomized controlled trial.pt.
62.	controlled clinical trial.pt.
63.	randomi#ed.ab.
64.	placebo.ab.
65.	randomly.ab.
66.	clinical trials as topic.sh.
67.	trial.ti.
68.	or/47-53
69.	Meta-Analysis/
70.	Meta-Analysis as Topic/
71.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
72.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
73.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
74.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
75.	(search* adj4 literature).ab.
76.	(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.
77.	cochrane.jw.
78.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
79.	or/55-64
80.	46 and (54 or 65)

1 **Embase (Ovid) search terms**

1.	*peroperative care/ or *intraoperative period/ or *perioperative nursing/ or *surgical patient/ or *intraoperative monitoring/
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.

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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.	exp echocardiography/
26.	impedance cardiography/
27.	((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 (echocardiogra* or doppler)).ti,ab.
28.	TEE.ti,ab.
29.	impedance plethysmography/
30.	((bioimpedance* or impedance*) adj (cardiograp* or plethysmogra* or phlebogra*)).ti,ab.
31.	((thoracic or transthoracic) adj electric* bioimpedance*).ti,ab.
32.	pulse wave/
33.	((pulse* or arterial) adj3 (contour or power or wave*)).ti,ab.
34.	dye dilution curve/
35.	((dye or indicator or lithium) adj3 dilut*).ti,ab.
36.	(electric* adj (cardiometry or velocimetry)).ti,ab.
37.	Pressure recording analy*.ti,ab.
38.	bioreactance*.ti,ab.
39.	hemodynamic monitoring/
40.	(h?emodynamic adj3 (output* or index or monitor* or measur* or record* or reading* or track* or assess*)).ti,ab.
41.	heart output/
42.	(cardiac adj3 (output* or index or monitor* or measur* or record* or reading* or track* or assess*)).ti,ab.
43.	or/25-42
44.	24 and 43
45.	random*.ti,ab.
46.	factorial*.ti,ab.
47.	(crossover* or cross over*).ti,ab.
48.	((doubl* or singl*) adj blind*).ti,ab.
49.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
50.	crossover procedure/
51.	single blind procedure/
52.	randomized controlled trial/

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53.	double blind procedure/
54.	or/45-53
55.	systematic review/
56.	Meta-Analysis/
57.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
58.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
59.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
60.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
61.	(search* adj4 literature).ab.
62.	(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.
63.	cochrane.jw.
64.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
65.	or/55-64
66.	44 and (54 or 65)

1 **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: [Echocardiography] explode all trees
#9.	MeSH descriptor: [Cardiography, Impedance] explode all trees
#10.	((oesophageal or esophageal or intra*esophageal or trans*esophageal) near/5 (echocardiogra* or doppler)):ti,ab
#11.	TEE:ti,ab
#12.	MeSH descriptor: [Plethysmography, Impedance] explode all trees
#13.	((bioimpedance* or impedance*) near/1 (cardiograp* or plethysmogra* or phlebogra*)):ti,ab
#14.	((thoracic or transthoracic) near/1 electric* bioimpedance*):ti,ab
#15.	MeSH descriptor: [Pulse Wave Analysis] explode all trees
#16.	((pulse* or arterial) near/3 (contour or power or wave*)):ti,ab
#17.	MeSH descriptor: [Dye Dilution Technique] explode all trees
#18.	((dye or indicator or lithium) near/3 dilut*):ti,ab
#19.	(electric* near/1 (cardiometry or velocimetry)):ti,ab
#20.	(Pressure recording analy*):ti,ab
#21.	bioreactance*:ti,ab
#22.	MeSH descriptor: [Hemodynamic Monitoring] explode all trees
#23.	(h*emodynamic near/3 (output* or index or monitor* or measur* or record* or reading* or track* or assess*)):ti,ab

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#24.	MeSH descriptor: [Cardiac Output] explode all trees
#25.	(cardiac near/3 (output* or index or monitor* or measur* or record* or reading* or track* or assess*)):ti,ab
#26.	(or #8-#25)
#27.	#7 and #26

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 16: 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.

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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.

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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/

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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

1 **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*))

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#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

1

2

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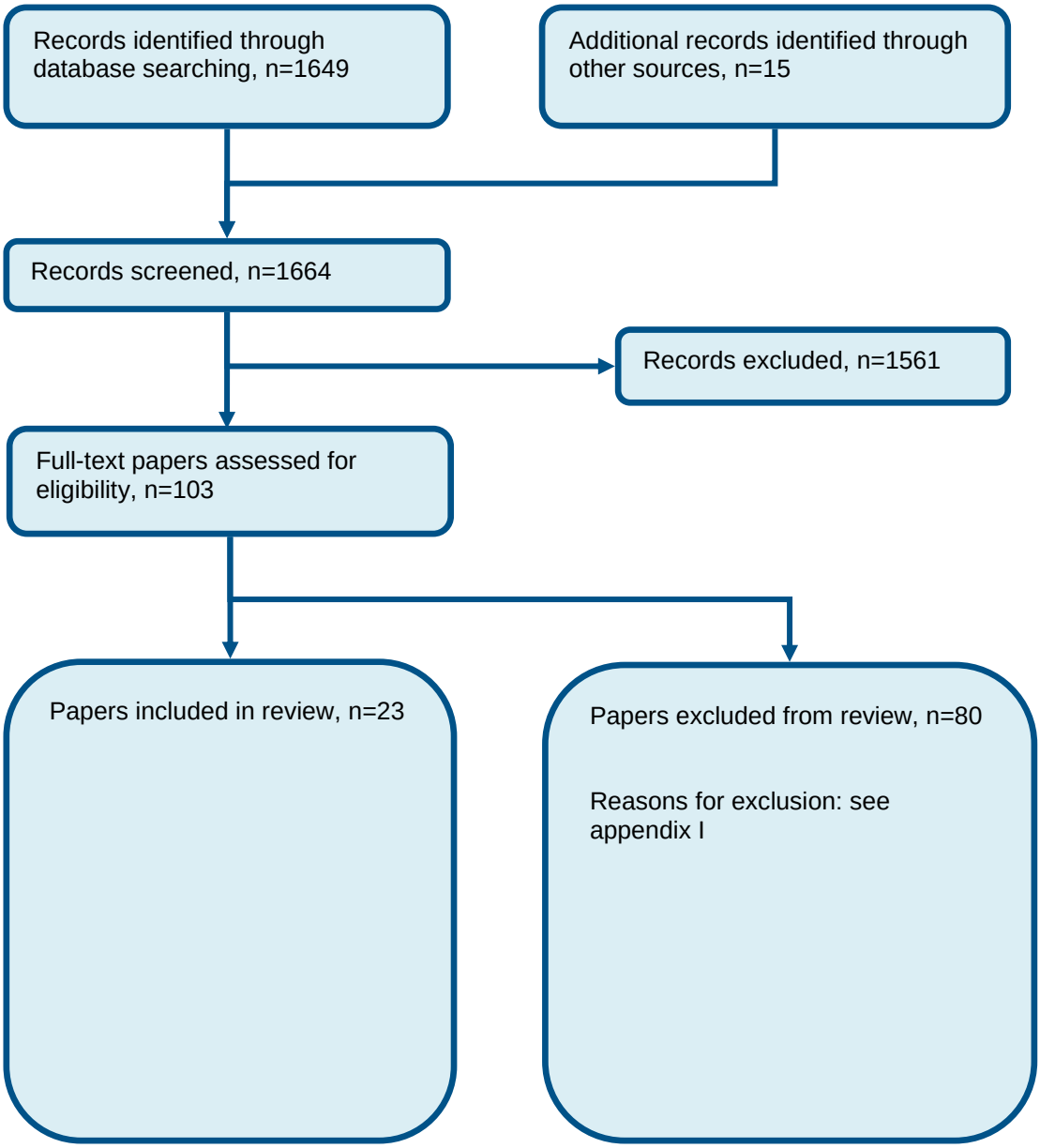
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of Cardiac Output Monitoring



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Appendix D: Clinical evidence tables

Study	Bartha 2013[3]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=149)
Countries and setting	Conducted in Sweden; Setting: Single centre, Helsinki
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients aged ≥70 yr and weight ≥40 kg who were undergoing proximal femoral fracture surgery
Exclusion criteria	patients who could be harmed due to the treatment (ongoing myocardial infarction, chronic dialysis), concomitant medication with lithium, known allergy to lithium or medical device components, weight ≤40 kg, life expectancy, 6 months, pathological fractures and conditions.
Recruitment/selection of patients	Consent from patients admitted for PFF
Age, gender and ethnicity	Age - Median (range): 85 (71-101). Gender (M:F): 40/109. Ethnicity: Not reported
Further population details	1. Age: >60 years (85 (71-101)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1: 3; ASA 2: 39; ASA 3: 86; ASA 4: 14). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (proximal femoral fracture surgery).
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Non-invasive cardiac output monitoring - oesophageal doppler monitor. Fluid challenge (3 ml kg21) with colloid was administered and repeated if a 10% increase in stroke volume (SV) was achieved. If no increase occurred, and if oxygen delivery (DO2I) was ,600 ml min21m22, then a dobutamine infusion was started at 0.2–10 mgkg21 min21. The infusion was stopped if tachycardia (.100 beats min21) occurred. Further fluid challenges were given if the SV decreased by 10%. The research team administered GDHT, which was discontinued at the end of the operation.. Duration of surgery. Concurrent medication/care: Between the admission to the hospital and operation, all patients received infusion of crystalloids based on individual assessment by the geriatricians. If no contraindication existed, then spinal anaesthesia was used for both groups: heavy bupivacaine 5 mg ml21, 1.5–2 ml (the

Study	Bartha 2013[3]
	lower limit of the dose recommendation for spinal anaesthesia was based on a Swedish trial done by Olofsson.15 The upper limit was used when surgery delay was presumed for various reasons.), and 1 ml sufentanil 5 mgml21.After anaesthesia, all patients received a background infusion of buffered glucose 25 mg ml21, at a rate of 1 ml kg21 h21 and Ringer's acetate, at a rate of 2 ml kg21 h21. The infusion was discontinued at the end of surgery. All patients were monitored with a lithium dilution cardiac output (CO) monitor (LiDCO, LiDCO Ltd, Sawston, Cambridge, UK), which was calibrated twice with i.v. lithium chloride (0.15 mmol ml21, 2 ml). These objectives were set for both groups (i) mean arterial pressure between 70 and 110 mm Hg and vasopressor support by phenylephrine or ephedrine, if the systolic arterial pressure declined by more than 30% from initial values, and (ii) haemoglobin concentration at or more than 100 g litre21. Haemodynamic data were saved on the LiDCO monitor. A research nurse documented all intra- and postoperative data (e.g. administered fluids, blood units, anaesthetics, and vasopressor support) in a case report form. All electronic data (e.g. haemodynamic data and blood-gases analyses) were collected and saved by intensive care unit pilot (Dipylon Medical AB, Solna, Sweden).. Indirectness: No indirectness (n=75) Intervention 2: Conventional clinical assessment. The attending anaesthesia team managed the routine fluid treatment. The research team assured adherence to the clinical programme. Ringer's acetate (300–500 ml) or colloids were administered before spinal anaesthesia. It was followed by the background infusion of buffered glucose and Ringer's acetate according to the treatment algorithm. Other fluids or vasopressor treatment (e.g. phenylephrine and ephedrine) for correction of decreasing arterial pressure were administered at the attending anaesthetist's discretion.. Duration of surgery. Concurrent medication/care: Between the admission to the hospital and operation, all patients received infusion of crystalloids based on individual assessment by the geriatricians. If no contraindication existed, then spinal anaesthesia was used for both groups: heavy bupivacaine 5 mg ml21, 1.5–2 ml (the lower limit of the dose recommendation for spinal anaesthesia was based on a Swedish trial done by Olofsson.15 The upper limit was used when surgery delay was presumed for various reasons.), and 1 ml sufentanil 5 mgml21.After anaesthesia, all patients received a background infusion of buffered glucose 25 mg ml21, at a rate of 1 ml kg21 h21 and Ringer's acetate, at a rate of 2 ml kg21 h21. The infusion was discontinued at the end of surgery. All patients were monitored with a lithium dilution cardiac output (CO) monitor (LiDCO, LiDCO Ltd, Sawston, Cambridge, UK), which was calibrated twice with i.v. lithium chloride (0.15 mmol ml21, 2 ml). These objectives were set for both groups (i) mean arterial pressure between 70 and 110 mm Hg and vasopressor support by phenylephrine or ephedrine, if the systolic arterial pressure declined by more than 30% from initial values, and (ii) haemoglobin concentration at or more than 100 g litre21. Haemodynamic data were saved on the LiDCO monitor. A research nurse documented all intra- and postoperative data (e.g. administered fluids, blood units, anaesthetics, and vasopressor support) in a case

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Study	Bartha 2013[3]
	report form. All electronic data (e.g. haemodynamic data and blood-gases analyses) were collected and saved by intensive care unit pilot (Dipylon Medical AB, Solna, Sweden).. Indirectness: No indirectness
Funding	Academic or government funding (Stockholm County)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus CONVENTIONAL CLINICAL ASSESSMENT Protocol outcome 1: Perioperative complications - Actual outcome: Patients with complications at 30 days; Group 1: 27/70, Group 2: 34/72 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: After assignment to a group, the treatment was not blinded to patients or operating theatre caregivers.; Group 1 Number missing: 5; Group 2 Number missing: 3 - Actual outcome: Total number of complications at 30 days; Group 1: 44/70, Group 2: 43/72 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: After assignment to a group, the treatment was not blinded to patients or operating theatre caregivers.; Group 1 Number missing: 5; Group 2 Number missing: 3 Protocol outcome 2: Length of hospital stay - Actual outcome: Length of hospital stay ; p: >0.05, Comments: Median (range) ODM: 10 (1-38); Routine: 9 (3-20)); 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: After assignment to a group, the treatment was not blinded to patients or operating theatre caregivers.; Group 1 Number missing: 5; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Length of stay in intensive care unit ; Hospital readmission

Study	Correa-Gallego 2015[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=135)
Countries and setting	Conducted in USA; Setting: Single centre.

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Study	Correa-Gallego 2015[22]
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Admission to discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All adult patients scheduled to undergo an open, elective liver resection (including those initially approached laparoscopically but converted to an open resection and those undergoing additional procedures).
Exclusion criteria	active coronary, cerebrovascular, or congestive heart disease; atrial fibrillation or flutter; clinically significant pulmonary insufficiency with a resting oxygen saturation < 90%; active renal dysfunction (serum creatinine > 1.8 mg/dL); evidence of severe hepatic dysfunction or portal hypertension (coagulopathy, thrombocytopenia, hypoalbuminemia, ascites); pregnancy; extreme body mass index (> 45 or < 17).
Recruitment/selection of patients	Patients admitted for surgery screened for eligibility.
Age, gender and ethnicity	Age - Mean (SD): 56.5 (13.5). Gender (M:F): 75/60. Ethnicity: Not reported
Further population details	1. Age: <60 years (56.5 (13.5)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA I-II: 78; ASA III-IV: 57). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (Elective liver resection).
Indirectness of population	No indirectness
Interventions	(n=69) Intervention 1: Non-invasive cardiac output monitoring - pulse pressure waveform analysis. At the completion of transection goal directed fluid management was initiated following an algorithm; 1:1 blood loss replacement with colloid, and albumin bolus infusions to restore SVV to a value ≤ 2 standard deviations from their baseline after induction. Crystalloid infusion was continued at 1ml/kg/hr.. Duration NA. Concurrent medication/care: All participants in the study received anesthesia from one of these practitioners, all of whom had had prior experience with the FloTrac sensor and SVV monitoring. All patients had continuous arterial waveform monitoring from the beginning of the operation and their SVV after induction (baseline) was recorded using the FloTrac sensor and EV1000 clinical platform (Edwards Lifesciences – Irvine, CA). Indirectness: No indirectness (n=66) Intervention 2: Conventional clinical assessment. Standard fluid management; 1:1 blood loss replacement with colloid, and crystalloid infusion at 6 ml/kg/hr of total operative time to restore the calculated insensible losses and maintenance requirements.. Duration NA. Concurrent medication/care: All participants in the study received anesthesia from one of these practitioners, all of whom had had prior experience with the FloTrac sensor and SVV monitoring. All patients

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Study	Correa-Gallego 2015[22]
	had continuous arterial waveform monitoring from the beginning of the operation and their SVV after induction (baseline) was recorded using the FloTrac sensor and EV1000 clinical platform (Edwards Lifesciences – Irvine, CA). Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULSE PRESSURE WAVEFORM ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT Protocol outcome 1: Mortality - Actual outcome: Mortality ; Group 1: 2/69, Group 2: 0/66 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: Length of hospital stay - Actual outcome: Length of stay ; Median (range) PPA: 7 (6-8); conventional: 6 (5-8); 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: Hospital readmission - Actual outcome: Readmission at 60 days; Group 1: 14/69, Group 2: 12/66 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 ; Perioperative complications ; Length of stay in intensive care unit

Study	Dhawan 2018[24]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in USA; Setting: Single centre.
Line of therapy	Not applicable

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Study	Dhawan 2018[24]
Duration of study	Intervention + follow up: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult (age >18), hemodynamically stable patients undergoing elective radical cystectomy
Exclusion criteria	Patient refusal, emergent surgery, preoperative mechanical ventilation, preoperative hemodynamic instability, and oesophageal or gastric pathology contraindicating insertion of the TEE probe.
Recruitment/selection of patients	Patients admitted for surgery screened for eligibility.
Age, gender and ethnicity	Age - Mean (SD): 67 (10). Gender (M:F): 58/19. Ethnicity: Not reported
Further population details	1. Age: >60 years (67 (10)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3. 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Major (Radical cystectomy).
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Non-invasive cardiac output monitoring - Transesophageal Echocardiography. Patients in the TEE group had TEE used throughout the intraoperative period to assist with fluid and hemodynamic management. The probe was removed before extubation. Duration NA. Concurrent medication/care: All participants in the study received a standardized general anaesthetic with radial artery blood pressure monitoring, with the goal of tracheal extubation in the operating room immediately following surgery. Anaesthetic technique in both groups was standardized to intravenous midazolam, fentanyl, propofol, hydromorphone, vecuronium, and inhaled desflurane in amounts appropriate for intraoperative tracheal extubation. Hemodynamic support for hypotension was standardized to intravenous ephedrine or phenylephrine as first-line agents, at the discretion of the anaesthesiologist, followed by other vasopressors (vasopressin and epinephrine) if necessary. Indirectness: No indirectness (n=39) Intervention 2: Conventional clinical assessment. While TEE was not routinely used in this group, it was allowed if requested by the general anaesthesiologist during the intraoperative period in a “rescue” role to evaluate life-threatening hemodynamic instability. Duration NA. Concurrent medication/care: All participants in the study received a standardized general anaesthetic with radial artery blood pressure monitoring, with the goal of tracheal extubation in the operating room immediately following surgery. Anaesthetic technique in both groups was standardized to intravenous midazolam, fentanyl, propofol, hydromorphone, vecuronium, and inhaled desflurane in amounts appropriate for intraoperative tracheal extubation. Hemodynamic support for hypotension was standardized to intravenous ephedrine or phenylephrine as first-line agents, at the discretion of the anaesthesiologist, followed by other vasopressors

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Study	Dhawan 2018[24]
	(vasopressin and epinephrine) if necessary. Indirectness: No indirectness
Funding	Nil
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULSE PRESSURE WAVEFORM ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT Protocol outcome 1: Mortality - Actual outcome: Mortality ; Group 1: 0/38, Group 2: 1/39 Risk of bias: All domain - Low, 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 stay ; Group 1: 8 days (4) n=38, Group 2: 10 days (8) n=39 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Complication - Actual outcome: Perioperative complications; Group 1: 2/38, Group 2: 8/39 Risk of bias: All domain - Low, 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 ; Readmissions ; Length of stay in intensive care unit

Study	Feldheiser 2015[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=41)
Countries and setting	Conducted in Germany; Setting: Charité—University Medicine Berlin.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Admission to discharge

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Study	Feldheiser 2015[28]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients were aged at least 18 years and undergoing elective liver resection (hemihepatectomy or extended liver resection).
Exclusion criteria	age less than 18 years, pregnancy or lactation, being unable or unwilling to give written consent to data storage and processing within clinical studies, member of staff of the Charité, simultaneous participation in another study, accommodation in an institution due to an official or judicial order, advanced disease, or operations within the last two months of the oesophagus of nasopharyngeal cavity, history of bleeding tendency, neurological or psychiatric disease, unclear history of alcohol related disorder, chronic heart failure class IV according to the New York Heart Association (NYHA), American Society of Anaesthesiologists (ASA) classification over III, renal insufficiency with dependency on haemodialysis, pulmonary oedema in the preoperative chest X-ray, allergy to gelatine, history of intracranial haemorrhage within one year before participation in the study before inclusion.
Recruitment/selection of patients	Patients admitted to Charité—University Medicine Berlin.
Age, gender and ethnicity	Age - Median (IQR): OD: 69 (56-75); PPA: 52 (41-65). Gender (M:F): 11/10. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (OD: 69 (56-75); PPA: 52 (41-65)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I: 2; ASA II: 9; ASA III: 9). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (elective liver resection).
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Non-invasive cardiac output monitoring - oesophageal doppler monitor. CardioQ-ODM shown to the treating personnel and the goal-directed algorithm was performed according to the values measured by the ODM.. Duration of surgery. Concurrent medication/care: The goal-directed algorithm guides the administration of intravenous colloid solution to maintain preload, the titration of norepinephrine to maintain arterial blood pressure and if necessary the titration of enoximone or nitroglycerine to lower central venous pressure.. Indirectness: No indirectness Comments: Blinded measurements of the PPA were performed by study personnel. (n=13) Intervention 2: Non-invasive cardiac output monitoring - pulse pressure waveform analysis. LiDCOrapid was shown to the treating personnel and the algorithm was performed according to the values

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Study	Feldheiser 2015[28]
	measured by the PPA.. Duration of surgery. Concurrent medication/care: The goal-directed algorithm guides the administration of intravenous colloid solution to maintain preload, the titration of norepinephrine to maintain arterial blood pressure and if necessary the titration of enoximone or nitroglycerine to lower central venous pressure.. Indirectness: No indirectness
Funding	Academic or government funding (Charité - Universitätsmedizin Berlin)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus PULSE PRESSURE WAVEFORM ANALYSIS Protocol outcome 1: Perioperative complications - Actual outcome: Patients with complications; Group 1: 6/11, Group 2: 9/10 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 ; Baseline details: Median age (IQR): ODM: 69 (56-75); PPA: 52 (41-65); Group 1 Number missing: 2, Reason: surgical procedure was changed after laparotomy; Group 2 Number missing: 3, Reason: surgical procedure was changed after laparotomy Protocol outcome 2: Length of hospital stay - Actual outcome: Length of hospital stay; Median (IQR): ODM 13 (12-19); usual care: 13 (9.75-22.5) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Median age (IQR): ODM: 69 (56-75); PPA: 52 (41-65); Group 1 Number missing: 2, Reason: surgical procedure was changed after laparotomy; Group 2 Number missing: 3, Reason: surgical procedure was changed after laparotomy	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Length of stay in intensive care unit ; Hospital readmission

Study	Hand 2016[36]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=94)
Countries and setting	Conducted in USA; Setting: Oncology setting, Medical University of South Carolina.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Length of hospital stay
Method of assessment of guideline	Adequate method of assessment/diagnosis

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Study	Hand 2016[36]
condition	
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients scheduled for primary free tissue transfer reconstruction with head and neck oncologic surgeons were enrolled.
Exclusion criteria	Cognitive limitations, cognitive heart failure, pulmonary disease, weight <55kg or >160kg, active cardiac dysrhythmia
Recruitment/selection of patients	Recruited by surgeons.
Age, gender and ethnicity	Age - Mean (SD): 58.4 (13). Gender (M:F): 70/24. Ethnicity: White: 76; African American: 13; Other: 5
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 2: 16; ASA 3: 73; ASA 4: 2). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (Head and Neck surgery).
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Non-invasive cardiac output monitoring - pulse pressure waveform analysis. Goal-directed haemodynamic therapy using Vigileo and EV-1000 (Edwards Lifescience). Measures BP, SV variation, cardiac index, and systemic vascular resistance. Hypotension defined as man arterial pressure <75mm Hg or >10% below baseline. Treatment algorithm dictates no action or treatment with IVF bolus, dobutamine, epinephrine or phenylephrine.. Duration of surgery. Concurrent medication/care: Pre-operative management in both groups was identical in terms of testing, medical optimisation and anaesthesia. . Indirectness: No indirectness (n=47) Intervention 2: Conventional clinical assessment. Standard management of hypotension, utilising only IV fluids (crystalloid and colloid). Goal BP was set as mean arterial pressure >70 or within 20% of baseline. . Duration of surgery. Concurrent medication/care: Pre-operative management in both groups was identical in terms of testing, medical optimisation and anaesthesia. . Indirectness: No indirectness
Funding	Study funded by industry (Part funded by Edwards Lifesciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULSE PRESSURE WAVEFORM ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Perioperative complications
- Actual outcome: Complications at period.; There were no complications related to placement or use of central venous or arterial catheter.

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Study	Hand 2016[36]
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: Study was not blinded; Protocol outcome 2: Length of hospital stay - Actual outcome: Length of hospital stay (days) at period.; Group 1: mean 9.11 days (SD 5.76); n=47, Group 2: mean 10.8 days (SD 7.65); n=47 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: Study was not blinded; Protocol outcome 3: Length of stay in intensive care unit - Actual outcome: Length of stay in ICU (days) at period.; Group 1: mean 1.88 days (SD 2.01); n=47, Group 2: mean 2.64 days (SD 2.49); n=47 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: Study was not blinded;	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Hospital readmission

Study	Kapoor 2016[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=130)
Countries and setting	Conducted in India; Setting: two cardiac surgical centres
Line of therapy	Not applicable
Duration of study	Intervention time: Admission to discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients of either sex with a European system for cardiac operative risk evaluation ≥3 undergoing coronary artery bypass grafting.
Exclusion criteria	Patients with cardiac dysrhythmias and contraindication to the central venous cannulation were excluded from the study. Patients requiring the initiation of intra-aortic balloon pump (IABP) therapy were excluded from the study because the FloTrac™ is not equipped to identify the waveforms of arterial pressure waveform while using IABP.

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Study	Kapoor 2016[40]
Recruitment/selection of patients	Patients admitted to cardiac surgery centre recruited
Age, gender and ethnicity	Age - Mean (SD): 61.2 (5.4). Gender (M:F): 82/38. Ethnicity:
Further population details	1. Age: >60 years (61.2 (5.4)). 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: (coronary artery bypass grafting.).
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Non-invasive cardiac output monitoring - pulse pressure waveform analysis. Standard haemodynamic monitoring. In addition, the cardiac index using FloTrac/volumeView set (Edwards Life Sciences Ltd.) and the continuous central venous oxygen saturation using PreSep catheter were monitored. A VolumeView™ cardiac output monitoring sensor was connected to the radial arterial cannula. PreSep™ catheter (continuous central venous oximetry) was inserted. If the CI was <2.5 L/min/m2, CVP <6 mmHg, or SVV >10%, fluids were given intravenously until the target CVP and SVV levels were achieved. . Duration of surgery . Concurrent medication/care: Electrocardiogram (ECG), oxygen saturation (SpO2), invasive blood pressure, central venous pressure (CVP) and arterial blood gas (ABG), urine output, and EtCO2 monitoring were common to both the groups.. Indirectness: No indirectness (n=60) Intervention 2: Conventional clinical assessment. Standard haemodynamic monitoring onl; Electrocardiogram (ECG), oxygen saturation (SpO2), invasive blood pressure, central venous pressure (CVP) and arterial blood gas (ABG), urine output, and EtCO2 monitoring were common to both the groups. All patients received fluids to maintain the CVP between 6 and 8 mmHg and MAP was maintained between 90 and 105 mmHg using inotropic agents and vasodilators.. Duration of surgery. Concurrent medication/care: Induction and maintenance of general anaesthesia was done in accordance with the institutional protocol.. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULSE PRESSURE WAVEFORM ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality ; Group 1: 2/60, Group 2: 6/60
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 outcome 2: Length of hospital stay

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Study	Kapoor 2016[40]
- Actual outcome: Length of hospital stay ; Group 1: mean 7.17 days (SD 1.93); n=60, Group 2: mean 7.94 days (SD 1.64); n=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 outcome 3: Length of stay in intensive care unit - Actual outcome: Length of ICU stay ; Group 1: mean 3.41 days (SD 0.75); n=60, Group 2: mean 3.94 days (SD 0.59); n=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 ; Perioperative complications ; Hospital readmission

Study	Lai 2015[43]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=220)
Countries and setting	Conducted in United Kingdom; Setting: Derriford Hospital, Plymouth
Line of therapy	Unclear
Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Consecutive eligible patients were recruited
Age, gender and ethnicity	Age - Mean (SD): 63 (15). Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Age: >60 years (63 (15)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1: 29; ASA 2: 153; ASA ≥3: 36). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (major elective rectal resection or cystectomy).
Indirectness of population	No indirectness
Interventions	(n=110) Intervention 1: Non-invasive cardiac output monitoring - pulse pressure waveform analysis. A

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Study	Lai 2015[43]
	medically qualified investigator monitored patients throughout surgery with a LiDCOrapid. The concealed investigator administered warmed colloid fluid challenges with Gelofusine directed by an algorithm to achieve an SVV goal of less than 10% throughout surgery.. Duration of surgery. Concurrent medication/care: All patients received general anaesthesia, conducted at the discretion of the consultant anaesthetist.. Indirectness: No indirectness. (n=111) Intervention 2: Conventional clinical assessment. All patients received mechanical ventilation whilst under general anaesthesia; tidal volume was not protocolised. The anaesthetist administered intraoperative crystalloid, colloid, blood products, and inotropes or vasopressors based on estimated patient requirements, losses, and standard haemodynamic variables. All participants had arterial line monitoring. Central venous pressure monitoring was permitted. Standard fluid therapy was not defined, but a general recommendation was made that perioperative fluid excess should be avoided. . Duration of surgery. Concurrent medication/care: All patients received general anaesthesia, conducted at the discretion of the consultant anaesthetist. Indirectness: No indirectness
Funding	Academic or government funding (National Institute for Academic Anaesthesia; National Institute of Healthcare Research; Bowel Cancer West)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULSE PRESSURE WAVEFORM ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 30 days; Group 1: 3/109, Group 2: 2/111
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: Concealed researcher administered extra fluid. SHam fluid used for control group.; Group 1 Number missing: 1, Reason: Declined surgery; Group 2 Number missing:
- Actual outcome: Mortality at 90 days; Group 1: 3/109, Group 2: 3/111
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: Concealed researcher administered extra fluid. SHam fluid used for control group.; Group 1 Number missing: 1, Reason: Declined surgery; Group 2 Number missing:

Protocol outcome 2: Perioperative complications
- Actual outcome: POMS ≥1 at 3 days; Group 1: 89/109, Group 2: 81/111

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Study	Lai 2015[43]
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: Concealed researcher administered extra fluid. SHam fluid used for control group.; Group 1 Number missing: 1, Reason: Declined surgery; Group 2 Number missing: - Actual outcome: POMS ≥1 at 5 days; Group 1: 55/109, Group 2: 54/111 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: Concealed researcher administered extra fluid. SHam fluid used for control group.; Group 1 Number missing: 1, Reason: Declined surgery; Group 2 Number missing: - Actual outcome: POMS ≥1 at 8 days; Group 1: 40/109, Group 2: 32/111 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: Concealed researcher administered extra fluid. SHam fluid used for control group.; Group 1 Number missing: 1, Reason: Declined surgery; Group 2 Number missing: Protocol outcome 3: Length of hospital stay - Actual outcome: Length of hospital stay ; Group 1: mean 11.8 days (SD 11.5); n=109, Group 2: mean 9.6 days (SD 6.8); n=111 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: Concealed researcher administered extra fluid. SHam fluid used for control group.; Group 1 Number missing: 1, Reason: Declined surgery; Group 2 Number missing: Protocol outcome 4: Hospital readmission - Actual outcome: 30 day readmission at 30 days; Group 1: 11/109, Group 2: 9/111 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: Concealed researcher administered extra fluid. SHam fluid used for control group.; Group 1 Number missing: 1, Reason: Declined surgery; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Length of stay in intensive care unit

Study	Mayer 2010[53]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in USA; Setting: Secondary care, single centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Admission to discharge
Method of assessment of guideline	Adequate method of assessment/diagnosis

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Study	Mayer 2010[53]
condition	
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA status of III with two or more risk factors according to risk index of Lee undergoing open major abdominal surgery (intestine resection, gastric resection, liver resection, esophageal resection, Whipple)
Exclusion criteria	under 18 years, patients with severe aortic regurgitation, permanent cardiac arrhythmias, intra-aortic balloon pump and patients undergoing emergency surgery.
Recruitment/selection of patients	Patients recruited from admission
Age, gender and ethnicity	Age - Mean (range): 72.5 (68-78). Gender (M:F): 42/18. Ethnicity:
Further population details	1. Age: >60 years (72.5 (68-78)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (intestine resection, gastric resection, liver resection, esophageal resection, Whipple).
Extra comments	Risk factors : 1. High-risk type of surgery 2. Ischemic heart disease 3. History of congestive heart failure 4. History of cerebrovascular disease 5. Insulin therapy for diabetes 6. Preoperative serum creatinine > 2.0 mg/dl.
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Non-invasive cardiac output monitoring - pulse pressure waveform analysis. Standard monitoring plus enhanced hemodynamic monitoring with the FloTrac/Vigileo device and an attempted cardiac index of at least 2.5 L·min-1·m-2. The arterial line was connected to the Vigileo monitor via the FloTrac pressure transducer. The shape of the arterial curve was checked visually for damping throughout the study period. CI, stroke volume index (SVI), as an indicator for fluid status, and stroke volume variation, (SVV) as an indicator for fluid responsiveness during mechanical ventilation and sinus rhythm, were continuously measured. Blood loss was substituted with fluids according to an algorithm and a hemoglobin value below 8 mg dL-1 was considered to be a trigger for transfusion of packed red blood cells. . Duration of surgery. Concurrent medication/care: premedication consisted of midazolam (0.01 mg kg-1), and standard general anesthesia was induced with fentanyl 1 to 2 µgkg-1,propofol1.5 to 2mgkg-1 and cisatracrurium 0.07 mg kg-1.. Indirectness: No indirectness (n=30) Intervention 2: Conventional clinical assessment.

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Study	Mayer 2010[53]
	Standard monitoring included electrocardiogram, invasive arterial blood pressure via right or left radial artery, CVP, pulse oximetry, temperature, inspiratory and expiratory gas concentrations. MAP was kept between 65 and 90 mmHg, CVP between 8 and 12 mmHg and urinary output more than 0.5 mL kg-1 h-1. Duration of surgery. Concurrent medication/care: premedication consisted of midazolam (0.01 mg kg-1), and standard general anesthesia was induced with fentanyl 1 to 2 µgkg-1,propofol1.5 to 2mgkg-1 and cisatracrurium 0.07 mg kg-1.. Indirectness: No indirectness
Funding	Study funded by industry (Edwards Lifescience)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULSE PRESSURE WAVEFORM ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality at Perioperative; Group 1: 2/30, Group 2: 2/30
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: senior anesthesiologists and senior surgeons blinded to group allocation and study design using standard predefined criteria;

Protocol outcome 2: Perioperative complications
- Actual outcome: Complications at Perioperative; Group 1: 17/30, Group 2: 49/30
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: senior anesthesiologists and senior surgeons blinded to group allocation and study design using standard predefined criteria;
- Actual outcome: Patients with complications at Perioperative; Group 1: 6/30, Group 2: 15/30
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: senior anesthesiologists and senior surgeons blinded to group allocation and study design using standard predefined criteria;

Protocol outcome 3: Length of hospital stay
- Actual outcome: Patients with complications at Perioperative; p: 0.006 days, Comments: Median (IQR)
PPA: 15 (12-17.75); control: 19 (14-23.5));
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: senior anesthesiologists and senior surgeons blinded to group allocation and study design using standard predefined criteria;

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Study	Mayer 2010[53]
Protocol outcomes not reported by the study	Quality of life ; Length of stay in intensive care unit ; Hospital readmission

Study	Moppett 2015[59]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=130)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Length 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 admitted through the emergency department with primary fragility hip fracture, aged over 60 who were listed for surgical repair under spinal anaesthesia.
Exclusion criteria	planned general anaesthetic for surgery repair; severe valvular heart disease (as this could affect the accuracy of the LiDCO device); taking therapeutic lithium (as this can affect the calibration of the LiDCO device); multiple injuries; and revision hip surgery or requirement for total hip arthroplasty.
Recruitment/selection of patients	Patients admitted through the emergency department recruited
Age, gender and ethnicity	Age - Median (range): 85 (63-95). Gender (M:F): 37/107. Ethnicity: Not reported
Further population details	1. Age: >60 years (85 (63-95)). 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: (hip fracture surgery).
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: Non-invasive cardiac output monitoring - systems based on pulse contour analysis and dye dilution. A LiDCO monitor was attached and calibrated, the use of vasoactive agents was at the discretion of the attending anaesthetist, as was target arterial pressure during surgery. Also received targeted i.v. colloid boluses [Gelofusine; B.Braun Medical, Sheffield, UK, or Geloplasma; Fresenius Kabi, Runcorn, UK (one patient)] using invasive pulse contour analysis continuous cardiac output monitoring to optimize SV. Boluses of 250 ml were given and the SV response was recorded.

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Study	Moppett 2015[59]
	If a response was recorded (SV increase >10%), a further bolus was given. If no response (SV did not increase or increased <10%), no further bolus was given unless the SV decreased by 10%. The attending anaesthetist was aware of the fluids being given.. Duration of surgery. Concurrent medication/care: expedited admission for patients when possible; i.v. fluids (0.9% saline) from time of admission until surgery; orthogeriatric assessment within 48 h of admission with combined orthopaedic and orthogeriatric postoperative care; surgery on dedicated, scheduled orthopaedic trauma lists with senior surgical and anaesthetic care; standardized surgical repairs: internal fixation for undisplaced intracapsular fractures; cemented hemiarthroplasty for displaced intracapsular fractures; dynamic hip screw for extracapsular neck fractures, and intramedullary nails for reverse oblique and subtrochanteric fractures; postoperative mobilization is attempted with all patients within 24 h of surgery; all patients receive routine prophylactic antibiotics and thromboprophylaxis.. Indirectness: No indirectness (n=68) Intervention 2: Conventional clinical assessment. A LiDCO monitor was attached and calibrated, the use of vasoactive agents was at the discretion of the attending anaesthetist, as was target arterial pressure during surgery. Operative anaesthetists were not allowed to view the LiDCO monitor for patients in the control group unless they believed that there was a strong clinical need to do so. . Duration of surgery. Concurrent medication/care: expedited admission for patients when possible; i.v. fluids (0.9% saline) from time of admission until surgery; orthogeriatric assessment within 48 h of admission with combined orthopaedic and orthogeriatric postoperative care; surgery on dedicated, scheduled orthopaedic trauma lists with senior surgical and anaesthetic care; standardized surgical repairs: internal fixation for undisplaced intracapsular fractures; cemented hemiarthroplasty for displaced intracapsular fractures; dynamic hip screw for extracapsular neck fractures, and intramedullary nails for reverse oblique and subtrochanteric fractures; postoperative mobilization is attempted with all patients within 24 h of surgery; all patients receive routine prophylactic antibiotics and thromboprophylaxis.. Indirectness: No indirectness
Funding	Academic or government funding (National Institute for Health Research (NIHR) under its Research for Patient Benefit Programme)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SYSTEMS BASED ON PULSE CONTOUR ANALYSIS AND DYE DILUTION versus CONVENTIONAL CLINICAL ASSESSMENT	

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Study	Moppett 2015[59]
Protocol outcome 1: Mortality - Actual outcome: Mortality at 12 months; Cumulative survival for control and LiDCO-guided groups. There was no significant difference (P=0.148) with outcomes adjusted for NHFS or age. Values reported on Kaplan Meier curve.; 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: The attending anaesthetist was aware of treatment allocation. Staff involved in postoperative care and discharge planning were unaware of treatment allocation. Data extraction from notes was done by staff unaware of treatment allocation and data analysis was performed before unblinding the trial.; Group 1 Number missing: 11, Reason: 4 failed arterial lines, 4 failed spinals, 1 withdrew consent, 1 protocol violation, 1 LiDCO failed to calibrate; Group 2 Number missing: 5, Reason: 3 failed spinals, 1 conversion to GA, 1 failed arterial line Protocol outcome 2: Perioperative complications - Actual outcome: Patients experiencing complications at Post-operative period; Group 1: 27/51, Group 2: 37/63 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: The attending anaesthetist was aware of treatment allocation. Staff involved in postoperative care and discharge planning were unaware of treatment allocation. Data extraction from notes was done by staff unaware of treatment allocation and data analysis was performed before unblinding the trial.; Group 1 Number missing: 11, Reason: 4 failed arterial lines, 4 failed spinals, 1 withdrew consent, 1 protocol violation, 1 LiDCO failed to calibrate; Group 2 Number missing: 5, Reason: 3 failed spinals, 1 conversion to GA, 1 failed arterial line - Actual outcome: Total complications at Post-operative period; Group 1: 63/51, Group 2: 89/63 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: The attending anaesthetist was aware of treatment allocation. Staff involved in postoperative care and discharge planning were unaware of treatment allocation. Data extraction from notes was done by staff unaware of treatment allocation and data analysis was performed before unblinding the trial.; Group 1 Number missing: 11, Reason: 4 failed arterial lines, 4 failed spinals, 1 withdrew consent, 1 protocol violation, 1 LiDCO failed to calibrate; Group 2 Number missing: 5, Reason: 3 failed spinals, 1 conversion to GA, 1 failed arterial line Protocol outcome 3: Length of hospital stay - Actual outcome: Length of hospital stay ; Group 1: mean 15.3 days (SD 5.33); n=51, Group 2: mean 14.2 days (SD 5.16); n=63 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: The attending anaesthetist was aware of treatment allocation. Staff involved in postoperative care and discharge planning were unaware of treatment allocation. Data extraction from notes was done by staff unaware of treatment allocation and data analysis was performed before unblinding the trial.; Group 1 Number missing: 11, Reason: 4 failed arterial lines, 4 failed spinals, 1 withdrew consent, 1 protocol violation, 1 LiDCO failed to calibrate; Group 2 Number missing: 5, Reason: 3 failed spinals, 1 conversion to GA, 1 failed arterial line
Protocol outcomes not reported by the study	Quality of life ; Length of stay in intensive care unit ; Hospital readmission

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Study	Noblett 2006[67]
Study type	RCT
Number of studies (number of participants)	(n=108)
Countries and setting	Conducted in United Kingdom; Setting: Surgical department of UK hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Length of hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients undergoing colorectal resection.
Exclusion criteria	Severe oesophageal disease, oesophageal or upper airway surgery, systemic steroid medication, moderate or severe aortic valve disease, bleeding diathesis and patient choice.
Recruitment/selection of patients	Consecutive patients recruited
Age, gender and ethnicity	Age - Mean (SD): 64.9 (14.6). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Age: >60 years (64.9 (14.6)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (Mean: 2.2). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (colorectal resection).
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Non-invasive cardiac output monitoring - oesophageal doppler monitor. Oesophageal Doppler monitoring (Cardiac-Q). Crystalloid, colloid or blood products administered by the anesthetist based on intraoperative losses and standard paramenters. Patients received an additional colloid (Volpex) bolus to maintain a descending aortic corrected flow time of more than 0.35 seconds and further bolus given to optimise the stroke volume. Further bolus only given if SV fell below 10% or FTc fell below 0.35 seconds. Routine perioperative monitoring included ECG, pulse oximetry, end-tidal carbon dioxide monitoring, and non-invasive BP monitoring.. Duration of surgery. Concurrent medication/care: All patients received a standard volatile-based GA. Indirectness: No indirectness Comments: All patients had oesophageal Doppler monitors, but fluid administration for the intervention group was based solely on the Doppler-assessed parameters, following a strict algorithm. (n=54) Intervention 2: Conventional clinical assessment. Routine perioperative monitoring included ECG, pulse oximetry, end-tidal carbon dioxide monitoring, and non-invasive BP monitoring. Crystalloid, colloid or

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Study	Noblett 2006[67]
	blood products administered by the anaesthetist based on intraoperative losses and standard parameters. . Duration of surgery. Concurrent medication/care: All patients received a standard volatile-based GA. Indirectness: No indirectness Comments: All patients had oesophageal Doppler monitors.
Funding	Academic or government funding (Royal College of Surgeons Research Fellowship Scheme)
Protocol outcome 1: Mortality - Actual outcome: Mortality; Group 1: 0/51, Group 2: 1/54 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: 3, Reason: Anaesthetists choice (3); Group 2 Number missing: 2, Reason: Anaesthetists choice (1), patient choice (1). Protocol outcome 2: Perioperative complications - Actual outcome: Complications at 45 days; Group 1: 12/51, Group 2: 19/52 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: 3, Reason: Anaesthetists choice (3); Group 2 Number missing: 2, Reason: Anaesthetists choice (1), patient choice (1). Protocol outcome 3: Length of hospital stay - Actual outcome: Length of stay at 30 days; p: 0.05, Comments: Median (range) ODM: 7 (3-35); Conventional care: 9 (4-45) 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: 3, Reason: Anaesthetists choice (3); Group 2 Number missing: 2, Reason: Anaesthetists choice (1), patient choice (1). Protocol outcome 4: Hospital readmission - Actual outcome: Readmissions at 45 days; Group 1: 0/51, Group 2: 1/52 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: 3, Reason: Anaesthetists choice (3); Group 2 Number missing: 2, Reason: Anaesthetists choice (1), patient choice (1).	
Protocol outcomes not reported by the study	Quality of life ; Length of stay in intensive care unit

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Study	Pearse 2014[71]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=734)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care; elective surgery
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 50 years or older undergoing major gastrointestinal surgery.
Exclusion criteria	Refusal of consent, pregnancy, acute pulmonary edema (within prior 7 days), acute myocardial ischemia (within prior 30 days), and surgery for palliative treatment only.
Recruitment/selection of patients	Recruited from patient admission
Age, gender and ethnicity	Age - Mean (SD): 71.8 years (8.5). Gender (M:F): 466/267. Ethnicity: Not reported
Further population details	1. Age: >60 years (71.8 years (8.5)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1: 45; ASA 2: 374; ASA 3: 278; ASA 4: 12). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (major gastrointestinal surgery).
Indirectness of population	No indirectness
Interventions	(n=368) Intervention 1: Non-invasive cardiac output monitoring - systems based on pulse contour analysis and dye dilution. Received intravenous fluid and inotropes according to a cardiac output–guided hemodynamic therapy algorithm using a cardiac output monitor (LiDCOrapid). Intravenous colloid solution was administered in 250mL boluses to achieve and maintain a maximal value of stroke volume. . Duration of surgery. Concurrent medication/care: Perioperative treatment goals were flexibly defined for all patients to avoid both extremes of clinical practice and practice misalignment.. Indirectness: No indirectness (n=366) Intervention 2: Conventional clinical assessment. All patients received standard measures to maintain oxygenation, haemoglobin, core temperature, and HR. Additional fluid was administered at the

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Study	Pearse 2014[71]
	discretion of the treating clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate, and base excess. . Duration of surgery. Concurrent medication/care: Perioperative treatment goals were flexibly defined for all patients to avoid both extremes of clinical practice and practice misalignment.. Indirectness: No indirectness
Funding	Principal author funded by industry (Dr Pearse reports that he has received equipment loans from LiDCO Ltd and a research grant from Circassia Holdings Ltd and has performed consultancy work for Edwards Lifesciences, Covidien, and Massimo Inc. Dr Pearse and Dr Hinds report that they are named inventors on a lapsed patent application relating to the perioperative use of dopexamine. Dr Gillies reports that he has received an honorarium from LiDCO Ltd for organizing a teaching workshop. Dr Grocott reports that he has received unrestricted grant funding from Deltex Medical Ltd and fees for lecturing from Fresenius Kabi and Edwards Lifesciences.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SYSTEMS BASED ON PULSE CONTOUR ANALYSIS AND DYE DILUTION versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 30 days; Group 1: 12/366, Group 2: 11/364
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: 2, Reason: Withdrew consent; Group 2 Number missing: 2, Reason: Randomised in error, Withdrew consent.
- Actual outcome: Mortality at 180 days; Group 1: 28/363, Group 2: 42/361
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: 2, Reason: Withdrew consent; Group 2 Number missing: 2, Reason: Randomised in error, Withdrew consent.

Protocol outcome 2: Perioperative complications
- Actual outcome: Complications at 30 days; Group 1: 134/366, Group 2: 158/364
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: 2, Reason: Withdrew consent; Group 2 Number missing: 2, Reason: Randomised in error, Withdrew consent.

Protocol outcome 3: Length of hospital stay
- Actual outcome: Length of stay at 30 days; p: 0.05, Comments: Median (IQR)
GDT: 10 (7-14); Usual care: 11 (7-17));

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Study	Pearse 2014[71]
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: 2, Reason: Withdrew consent; Group 2 Number missing: 2, Reason: Randomised in error, Withdrew consent.	
Protocol outcomes not reported by the study	Quality of life ; Length of stay in intensive care unit ; Hospital readmission

Study	Pillai 2011[76]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=66)
Countries and setting	Conducted in United Kingdom; Setting: Oncology centre of hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Length 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 radical cystectomy as curative treatment for muscle invasive transitional cell carcinoma of the bladder.
Exclusion criteria	esophageal disease/stricture, recent esophageal or laryngeal surgery, aortic valve disease.
Recruitment/selection of patients	Recruited from hospital
Age, gender and ethnicity	Age - Mean (range): 67.5 (95% CI 63.2-71.5). Gender (M:F): 19/47. Ethnicity: Not reported
Further population details	1. Age: >60 years (mean 67.5). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (Mean (95% CI): 1.9 (1.7-2.1)). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (radical cystectomy).
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Non-invasive cardiac output monitoring - oesophageal doppler monitor. Standard respiratory and cardiovascular monitoring including BP. Standard intraoperative fluids at the discretion of the consultant anaesthetists, and additional fluid from a researcher via esophageal Doppler (Cardio-Q) following a set algorithm. Fluid given if SV increase by >10% and FTc <0.35 seconds. Duration of surgery. Concurrent medication/care: All patients received a standard GA. Indirectness: No indirectness

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Study	Pillai 2011[76]
	(n=34) Intervention 2: Conventional clinical assessment. Standard respiratory and cardiovascular monitoring including BP. Standard intraoperative fluids at the discretion of the consultant anaesthetists.. Duration of surgery . Concurrent medication/care: All patients received standard GA.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus CONVENTIONAL CLINICAL ASSESSMENT Protocol outcome 1: Perioperative complications - Actual outcome: Postoperative complication at NA; Group 1: 16/32, Group 2: 35/34; Comments: Complications: wound dehiscence, wound infection, ileus. 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 Protocol outcome 2: Length of hospital stay - Actual outcome: Length of hospital stay ; Group 1: mean 18 days (SD 10.3); n=32, Group 2: mean 22 days (SD 10.3); n=34 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 ;	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Length of stay in intensive care unit ; Hospital readmission

Study	Ramsingh 2013[80]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in USA; Setting: Secondary care, elective surgery
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

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Study	Ramsingh 2013[80]
Inclusion criteria	Patients scheduled for major abdominal, non-vascular surgery
Exclusion criteria	Age less than 18 years, coagulopathy, history of cerebrovascular disease, significant renal or hepatic dysfunction (creatinine >50 % or liver enzymes >50 % of normal values), history of congestive heart failure, ischemic heart disease, cardiac arrhythmias producing irregular rhythms, significant lung disease, and patient choice. Also, patients were excluded if they developed intraoperative arrhythmias of more than 4 non-sinus beats within a minute for a period of at least 5 min. Patients were excluded if they developed a condition requiring a second surgical procedure prior to return of GI function, since the urgent nature of the second surgery would interfere with interpretation of the impact of fluid management during the first surgery.
Recruitment/selection of patients	Patients scheduled for surgery approached for consent
Age, gender and ethnicity	Age - Mean (SD): 59.2 (16.9). Gender (M:F): 11/27. Ethnicity: Not reported
Further population details	1. Age: <60 years (59.2 (16.9)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (P-POSSUM used). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (major abdominal, non-vascular surgery).
Extra comments	Abdominal procedures were considered major if listed for resection of urologic, gastrointestinal or gynecologic cancers with tumor debulking, staging or reconstruction with a risk for significant surgical blood loss.
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Non-invasive cardiac output monitoring - pulse pressure waveform analysis. FloTrac/Vigileo system was used. GDT patients were managed by an SVV guided protocol to maintain SVV\12 %. . Duration of surgery. Concurrent medication/care: All patients had routine intraoperative monitoring per American Society of Anesthesiologists Guidelines. All patients were ventilated at 8 mL/kg of ideal body weight and their respiratory rate was adjusted such that they had minute ventilation of approximately 7–8 L/min with an I:E ratio of 1:2. Radial arterial catheters were placed in all patients because of the risk for significant surgical blood loss.. Indirectness: No indirectness (n=20) Intervention 2: Conventional clinical assessment. Control patients had fluid management guided by routine cardiovascular monitoring at the discretion of their Staff Anesthesiologist, who was blinded to SVV data. Control group anesthesiology teams were allowed to have the SVV information unblinded if needed for clinical decision-making but patients were removed from analysis if this occurred.. Duration of surgery. Concurrent medication/care: All patients had routine intraoperative monitoring per American Society of Anesthesiologists Guidelines. All patients were ventilated at 8 mL/kg of ideal body weight and their respiratory rate was adjusted such that they had minute ventilation of approximately 7–8 L/min with an I:E ratio of 1:2. Radial arterial catheters were placed in all patients because of the risk for significant surgical blood loss.. Indirectness: No indirectness

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Study	Ramsingh 2013[80]
Funding	Academic or government funding (supported by the Department of Anesthesiology, Loma Linda University School of Medicine, Loma Linda, CA, USA.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULSE PRESSURE WAVEFORM ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT Protocol outcome 1: Length of hospital stay - Actual outcome: Length of stay ; Median (IQR) GDT: 5.0 (3.75–8.25); Control: 7.5 (5.25–10.75); p=0.04; 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 ; Baseline details: No difference in P-POSSUM scores. Difference in age: GDT: 53.5 ± 16.2; Control: 64.4 ± 15.8; Blinding details: Surgical teams, intraoperative and postoperative nursing staff and patients were blinded to group assignment, but the anesthesiologist was aware of group designation.; Group 1 Number missing: 5, Reason: Did not receive allocated intervention (3), lost to follow-up (2); Group 2 Number missing: 3, Reason: Did not receive allocated intervention (2), lost to follow-up (1)	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Perioperative complications ; Length of stay in intensive care unit ; Hospital readmission

Study	Ratti 2016[81]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in Italy; Setting: Secondary care; Hepatobiliary surgery Division of San Raffaele Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for laparoscopic liver resection (LLR) for primary or secondary liver tumours.
Exclusion criteria	Associated major abdominal procedures (e.g. colorectal and/or pancreatic resections); repeated liver resections; single-port resections; patients under 18 years of age or unable to give their informed consent.

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Study	Ratti 2016[81]
Recruitment/selection of patients	Eligible admitted patients screened for enrolment
Age, gender and ethnicity	Age - Mean (SD): 59.5 (10). Gender (M:F): 45/45. Ethnicity: Not reported
Further population details	1. Age: <60 years (59.5 (10)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1: 14; ASA 2: 67; ASA 3: 9). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation:
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Non-invasive cardiac output monitoring - systems based on pulse contour analysis and dye dilution. In all patients ECG (electrocardiogram) and MAP (mean arterial blood pressure) were obtained using a radial or humeral catheterization, pulse oxymetry and diuresis were monitored.20 In the SVV group, arterial access was connected to the FloTrac sensor of the Vigileo monitor system (Edwards Lifesciences) to measure SVV. In this group SV (stroke volume), CO (cardiac output) and CI (cardiac index) were monitored; VO2 (oxygen consumption) and DO2 (oxygen delivery) were calculated on the basis of blood gas analysis which was repeated during surgery in both groups to check either the onset of acidosis or the level of haemoglobin.21 In the SVV group, the goal was to maintain SVV over 12% (at least among 12–15%) during resection.. Duration of surgery. Concurrent medication/care: General anaesthesia was performed in a standardized way, administering for induction intravenous fentanyl (2 mcg/kg) and propofol (2 mg/kg). Muscle relaxation was obtained with a bolus of non-depolarizing curare (cisatracurium or rocuronium at a dose of 0.5 mg/kg or 0.6 mg/kg respectively). All patients were mechanically ventilated with a tidal volume of 8 mL/kg without PEEP. Anaesthesia was maintained with inhaled halogenated gas (sevoflorane or desflorane titrated to minimal alveolar concentration). Indirectness: No indirectness (n=45) Intervention 2: Conventional clinical assessment. ECG and MAP were obtained using a radial or humeral catheterization, pulse oxymetry and diuresis were monitored. CVP was measured through a CVC inserted in the internal jugular vein after the induction of general anaesthesia. In this group SvO2 (oxygen venous saturation) was monitored as well. The goal was to maintain CVP under or equal to 5 cm H20. Hence, fluid therapy with crystalloids was guided by CVP values to achieve an hypovolaemic state.. Duration of surgery. Concurrent medication/care: General anaesthesia was performed in a standardized way, administering for induction intravenous fentanyl (2 mcg/kg) and propofol (2 mg/kg). Muscle relaxation was obtained with a bolus of non-depolarizing curare (cisatracurium or rocuronium at a dose of 0.5 mg/kg or 0.6 mg/kg respectively). All patients were mechanically ventilated with a tidal volume of 8 mL/kg without PEEP. Anaesthesia was maintained with inhaled halogenated gas (sevoflorane or desflorane titrated to minimal alveolar concentration). Indirectness: No indirectness
Funding	No funding

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Study	Ratti 2016[81]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SYSTEMS BASED ON PULSE CONTOUR ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT Protocol outcome 1: Mortality - Actual outcome: Mortality at 90 days; Group 1: 0/45, Group 2: 0/45 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: Perioperative complications - Actual outcome: Complications at 90 days; Group 1: 4/45, Group 2: 5/45 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 stay ; Median (range) SVV: 4 (2-10), CVP: 5 (3-13); 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 ; Length of stay in intensive care unit ; Hospital readmission

Study	Salzwedel 2013[84]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=160)
Countries and setting	Conducted in Germany; Setting: Secondary care; elective surgery
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing elective abdominal surgery including general, gynecological and urological surgery with

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Study	Salzwedel 2013[84]
	anticipated duration of surgery of more than 120 minutes or an estimated blood loss of more than 20% of blood volume, ASA classification 2 or 3, and an indication for an arterial line and central venous catheter.
Exclusion criteria	Planned postoperative high-care intensive care unit stay, pregnant or lactating woman, laparoscopic surgery and arrhythmias.
Recruitment/selection of patients	Patients admitted for surgery recruited
Age, gender and ethnicity	Age - Mean (SD): 64 (17.6). Gender (M:F): 97/63. Ethnicity: Not reported
Further population details	1. Age: <60 years (64 (17.6)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 2: 94; ASA 3: 66). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (abdominal surgery including general, gynecological and urological surgery).
Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: Non-invasive cardiac output monitoring - pulse pressure waveform analysis. Patients in the SG received basic anesthetic monitoring by five-lead-electrocardiogram, pulse oximetry and blood pressure cuff, at least one peripheral i.v., a central venous catheter and invasive radial arterial blood pressure monitoring. This arterial line was additionally connected to the cardiac index trending monitor (ProAQT, PULSION Medical Systems SE, Munich, Germany). First, preload was optimized by fluid loading until PPV was <10%. At this point, the patient's individual preload optimized CI was determined and used as the hemodynamic goal until the end of surgery.. Duration of surgery. Concurrent medication/care: All patients were monitored in the post-anesthetic care unit (PACU) until they were transferred to the ward.. Indirectness: No indirectness (n=81) Intervention 2: Conventional clinical assessment. Patients of the CG received basic anesthetic monitoring by five-lead-electrocardiogram, pulse oximetry and blood pressure cuff, at least one peripheral i.v., a central venous catheter and invasive radial arterial blood pressure monitoring.. Duration of surgery. Concurrent medication/care: All patients were monitored in the post-anesthetic care unit (PACU) until they were transferred to the ward.. Indirectness: No indirectness
Funding	Study funded by industry (unrestricted research grant from PULSION Medical Systems)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULSE PRESSURE WAVEFORM ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Perioperative complications
- Actual outcome: Total number of complications at 28 days; Group 1: 52/79, Group 2: 72/81

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Study	Salzwedel 2013[84]
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: Care providers and investigators could not be blinded due to the presence of the cardiac index trending.Twenty patients (overall) had to be excluded from the study and/or analysis because of various reasons. Protocol outcome 2: Length of hospital stay - Actual outcome: Length of hospital stay ; Group 1: mean 11 days (SD 8); n=79, Group 2: mean 10 days (SD 11.8); n=81 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: Care providers and investigators could not be blinded due to the presence of the cardiac index trending. Twenty patients (overall) had to be excluded from the study and/or analysis because of various reasons.	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Length of stay in intensive care unit ; Hospital readmission

Study	Senagore 2009[87]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=64)
Countries and setting	Conducted in USA; Setting: Secondary care; elective surgery.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Length 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 aged 18-90 years undergoing laparoscopic segmental colectomy.
Exclusion criteria	patients who had undergone major surgery in the last month, pregnant, minors, psychiatric patients, ASA grade 4, significant renal dysfuntion, heart failure, esophageal pathology.
Recruitment/selection of patients	Patients referred for surgery recruited
Age, gender and ethnicity	Age - Other: Not reproted. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA grade ≥4 excluded). 3. Surgery grade based on NICE preoperative tests for elective surgery

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Study	Senagore 2009[87]
	guideline categorisation: (laparoscopic segmental colectomy).
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Non-invasive cardiac output monitoring - oesophageal doppler monitor. Received standard anaesthesia and monitoring. A separate anaesthesia team administered Lactated Ringers bolus following an algorithm dictated by SVV as measured by ODM (CarioQ).. Duration of surgery. Concurrent medication/care: Received standard anaesthetic care. . Indirectness: No indirectness (n=22) Intervention 2: Conventional clinical assessment. Received maintenance fluids based on clinical evaluation of the anaesthesia team, based on urinary outputs, HR increase, BP decrease, or CVP decrease. . Duration of surgery. Concurrent medication/care: Received standard anaesthetic care. Indirectness: No indirectness
Funding	Study funded by industry (Educational grant from Deltex Medical)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus CONVENTIONAL CLINICAL ASSESSMENT Protocol outcome 1: Mortality - Actual outcome: Mortality at Perioperative period; Group 1: 0/21, Group 2: 0/22 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: Perioperative complications - Actual outcome: Complications at Perioperative period; Group 1: 41/21, Group 2: 40/22 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 Perioperative period; Mean; (p: <0.05) hours, Comments: ODM: 71.8; standard care: 64.9); 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 ; Length of stay in intensive care unit ; Hospital readmission

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Study	Shillcutt 2014[88]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=28)
Countries and setting	Conducted in USA; Setting: Secondary care; elective surgery
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 day follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged >65 years or aged >19 years with risk factors for left ventricular diastolic dysfunction undergoing non-cardiac surgery.
Exclusion criteria	Expected hospital stay <24 hours, suspicion of elevated ICP, preoperative shock or sepsis, emergency operation, ASA grade 5, GA not planned
Recruitment/selection of patients	Recruited from hospital admission
Age, gender and ethnicity	Age - Mean (SD): 69.7 (11.84). Gender (M:F): 10/18. Ethnicity: Not reported
Further population details	1. Age: >60 years (69.7 (11.84)). 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: (Orthopaedic: 9; General: 12; Vascular: 4; Thoracic: 3).
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Non-invasive cardiac output monitoring - trans-oesophageal echocardiography . Echocardiography-guided hemodynamic management. Received hemodynamic management of crystalloid or colloid fluid based on left ventricular filling patterns on transesophageal echocardiography, according to a predetermined algorithm. . Duration of surgery. Concurrent medication/care: .. Indirectness: No indirectness (n=14) Intervention 2: Conventional clinical assessment. Standard hemodynamic management using non-invasive blood pressure monitoring or invasive monitoring (arterial/central venous line) if so indicated by the anaesthetist. Target of keeping intraoperative BP within 10-15% of patient baseline readings. Fluids given as deemed appropriate by anaesthetist who were blinded to the study. . Duration of surgery. Concurrent medication/care: .. Indirectness: No indirectness

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Study	Shillcutt 2014[88]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANS-OESOPHAGEAL ECHOCARDIOGRAPHY versus CONVENTIONAL CLINICAL ASSESSMENT Protocol outcome 1: Length of hospital stay - Actual outcome: Length of hospital stay at 30 days; p: 0.058, Comments: Median (range) EGHEM: 3 (1-10); Conventional care: 5 (1-36)); 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 ;	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Perioperative complications ; Length of stay in intensive care unit ; Hospital readmission

Study	Smetkin 2009[91]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Russia; Setting: University Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients diagnosed with coronary artery disease, ranked ASA II-III, and scheduled for off-pump coronary artery bypass.
Exclusion criteria	Aged <18 years, severe cardiac valve dysfunction or peripheral artery disease, simultaneous intervention, or transfer to CPB.
Recruitment/selection of patients	Recruited from patients admitted for surgery
Age, gender and ethnicity	Age - Mean (SD): 56.7 (9.1). Gender (M:F): 32/8. Ethnicity: Not reported

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Study	Smetkin 2009[91]
Further population details	1. Age: <60 years (56.7 (9.1)). 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: (off-pump coronary artery bypass).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Non-invasive cardiac output monitoring - pulse pressure waveform analysis. Advanced monitoring: Therapy targeted according to intrathorcic blood volume index, cardiac index (PICCOplus), HR, MAP, and central venous oxygen saturation. Colloid/anesthesia maintained according to predetermined algorithm.. Duration of surgery. Concurrent medication/care: Establishment of routine hemodynamic monitoring with ECG, BP, and oxygen saturation. . Indirectness: No indirectness (n=21) Intervention 2: Conventional clinical assessment. Conventional monitoring: hemodynamic and fluid management was primarily based on CVP, HR, and MAP (LifeScope).. Duration of surgery. Concurrent medication/care: Establishment of routine hemodynamic monitoring with ECG, BP, and oxygen saturation. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PULSE PRESSURE WAVEFORM ANALYSIS versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Perioperative complications
- Actual outcome: Patients with postoperative complications at Until discharge; Group 1: 1/20, Group 2: 4/20
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 2: Length of hospital stay
- Actual outcome: Post-operative hospital stay ; p: <0.05 days, Comments: Median IQR
Advanced monitoring: 12 (8-19); Conventional care: 15 (13-24);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 3: Length of stay in intensive care unit
- Actual outcome: Post-operative ICU stay ; p: <0.05 hours, Comments: Median (IQR)
Advanced monitoring: 20 (18-23); Conventional care: 23 (21-38);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

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Study	Smetkin 2009[91]
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Hospital readmission

Study	Srinivasa 2013[93]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=85)
Countries and setting	Conducted in New Zealand; Setting: Secondary care; elective surgery.
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing elective open or laparoscopic colectomy for any indication.
Exclusion criteria	severe oesophageal disease, recent oesophageal or upper airway surgery, moderate or severe aortic valve disease on echocardiography, bleeding diathesis, regular use of corticosteroids or mineralocorticoids, cognitive impairment, American Society of Anesthesiologists grade IV or V, rectal tumour (less than 15 cm from the anal verge), stoma formation and patient choice.
Recruitment/selection of patients	Consecutive patients recruited
Age, gender and ethnicity	Age - Mean (SD): 70.5 (14). Gender (M:F): 41/33. Ethnicity: Not reported
Further population details	1. Age: >60 years (70.5 (14)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1: 10; ASA 2: 35; ASA 3: 29). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (elective open or laparoscopic colectomy for any indication.).
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Non-invasive cardiac output monitoring - oesophageal doppler monitor. Patients randomized to GDT were treated with a weight-based bolus of colloid was permitted based on cardiac function measured by means of an oesophageal Doppler monitor (CardioQ). An algorithm based on FTc and SV dictated fluid administration. . Duration of surgery. Concurrent medication/care: Also treated with baseline fluid restriction and a limit of 1500 ml crystalloid solution. All intravenous fluids were stopped by default when patients arrived on the ward.. Indirectness: No indirectness

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Study	Srinivasa 2013[93]
	(n=43) Intervention 2: Conventional clinical assessment. Patients randomized to fluid restriction were allowed to receive up to 1500 ml crystalloid solution (PlasmaLyteTM 148; Baxter Healthcare, Sydney, New South Wales, Australia) during surgery. They were also permitted to receive a total of 500 ml succinylated gelatine colloid solution (Gelofusine®; Braun, Sydney, New SouthWales, Australia) titrated by heart rate, blood pressure, urine output and invasive measures (arterial lines) when used.. Duration of surgery. Concurrent medication/care: All intravenous fluids were stopped by default when patients arrived on the ward. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (The ODM was lent by Pharmaco NZ for the duration of the study. All disposable probes were purchased at regular cost.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Perioperative complications
- Actual outcome: Patients with complications at 30 days; Group 1: 26/37, Group 2: 27/37
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: The patient, study investigators, surgeon and other medical staff responsible for patient care were blinded to patient allocation. All patients had the ODM probe inserted by a trained research assistant. The ODM monitor was covered to ensure blinding; Group 1 Number missing: 5, Reason: Stapler misfire (1); Rectal lesion found at operation (2); Poor vascularity of bowel on clinical assessment (2); Group 2 Number missing: 6, Reason: Unresectable lesion (1); Rectal lesion found at operation (4); Poor vascularity of bowel on clinical assessment (1).

Protocol outcome 2: Length of hospital stay
- Actual outcome: Patients with complications ; Median (range)
ODM: 6 (3-31); Conventional care: 5 (2-29);
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: The patient, study investigators, surgeon and other medical staff responsible for patient care were blinded to patient allocation. All patients had the ODM probe inserted by a trained research assistant. The ODM monitor was covered to ensure blinding; Group 1 Number missing: 5, Reason: Stapler misfire (1); Rectal lesion found at operation (2); Poor vascularity of bowel on clinical assessment (2); Group 2 Number missing: 6, Reason: Unresectable lesion (1); Rectal lesion found at operation (4); Poor vascularity of bowel on clinical assessment (1).

Protocol outcome 3: Hospital readmission
- Actual outcome: Readmissions at 30 days; Group 1: 9/37, Group 2: 4/37

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Study	Srinivasa 2013[93]
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: The patient, study investigators, surgeon and other medical staff responsible for patient care were blinded to patient allocation. All patients had the ODM probe inserted by a trained research assistant. The ODM monitor was covered to ensure blinding; Group 1 Number missing: 5, Reason: Stapler misfire (1); Rectal lesion found at operation (2); Poor vascularity of bowel on clinical assessment (2).; Group 2 Number missing: 6, Reason: Unresectable lesion (1); Rectal lesion found at operation (4); Poor vascularity of bowel on clinical assessment (1).	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Length of stay in intensive care unit

Study	Stens 2017[94]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=244)
Countries and setting	Conducted in The Netherlands; Setting: Hospital setting
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with elective moderate-risk abdominal surgery planned and aged 18–85 years. Moderate-risk surgery was defined as patients categorised as grade-2 risk according to the Modified Johns Hopkins Surgical Criteria (moderately to significantly invasive procedure, potential blood loss 500–1500 ml, or moderate risk to patient independent of anaesthesia).
Exclusion criteria	Pre-existing cardiac arrhythmia; emergency procedure; pre-operative admission to the intensive care unit (ICU); BMI < 20 kg.m・2 or > 40 kg.m・2; evidence of cardiac decompensation; aortic valve disease; ejection fraction < 0.3; aortic valve stenosis with valve area < 1.2 cm2; pulmonary arterial pressure > 30 mmHg; and tricuspid annular plane systolic excursion < 18 mm.
Recruitment/selection of patients	Recruited from patient admission
Age, gender and ethnicity	Age - Mean (SD): 63 (12.5). Gender (M:F): 97/78. Ethnicity: Not reported
Further population details	1. Age: >60 years (83 (65-102)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: 2 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Moderate

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Study	Stens 2017[94]
Indirectness of population	No indirectness
Interventions	(n=122) Intervention 1: Non-invasive cardiac output monitoring – pulse pressure analysis. The ccNexfin device (Edwards Lifesciences, Amsterdam, the Netherlands), a non-invasive continuous arterial blood pressure monitor, was used for PPV and CI measurements in all patients, and monitoring was instituted before the induction of anaesthesia. The Nexfin monitor derives a finger arterial blood pressure waveform by optical plethysmography using a blood pressure cuff according to the volume-clamp method. The Nexfin CO-trek algorithm is used to calculate SV and CI based on the arterial blood pressure waveform. A built-in expert system for calibration (Physiocal, BMEYE BV, Amsterdam, The Netherlands) adjusts the cuff to determine a proper volume-clamp set point, while a heart reference system is used to compensate for hydrostatic differences between the heart and finger cuff level. The anaesthetist was required to keep MAP > 70 mmHg, CI > 2.5 l min -1.m-2 and PPV < 12% using a predefined protocol. . Duration of surgery. Concurrent medication/care: The anaesthetic technique was left to the discretion of the attending anaesthetist. All patients had an arterial line inserted for continuous monitoring of MAP. Indirectness: No indirectness (n=122) Intervention 2: Conventional clinical assessment. The attending anaesthetist was blinded to the PPV/CI values and maintained target MAP values > 70 mmHg (as measured by the Nexfin device) with intravenous fluids of any type, vasopressors and/or inotropes, based on their clinical judgement. . Duration of surgery. Concurrent medication/care: The anaesthetic technique was left to the discretion of the attending anaesthetist. All patients had an arterial line inserted for continuous monitoring of MAP. Indirectness: No indirectness
Funding	All disposables were funded by the individual hospitals. No other external funding or competing interests declared.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 30 days; Group 1: 1/81, Group 2: 1/94
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

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Study	Stens 2017[94]
Protocol outcome 2: Perioperative complications - Actual outcome: Any complication within 30 days; Group 1: 38/81, Group 2: 42/94 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, 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 (median days, IQR) at NA; Group 1: 6 (4-11), Group 2: 6 (4-9) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 4: Length of ICU stay - Actual outcome: Length of hospital stay (median days, IQR) at NA; Group 1: 0 (0-0), Group 2: 0 (0-0) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 5: Hospital readmission - Actual outcome: Any readmission within 30 days; Group 1: 7/81, Group 2: 8/94 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Quality of life ;

Study	Venn 2002[100]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in United Kingdom; Setting: Hospital setting
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

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Study	Venn 2002[100]
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted with hip fracture.
Exclusion criteria	Aged <65 years, oesphogeal pathology, central venous cannula, pathological fracture of femur, regional anaesthesia.
Recruitment/selection of patients	recruited from patient admission
Age, gender and ethnicity	Age - Mean (range): 83 (65-102). Gender (M:F): 16/74. Ethnicity: Not reported
Further population details	1. Age: >60 years (83 (65-102)). 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: (Hip fracture surgery).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Non-invasive cardiac output monitoring - oesophageal doppler monitor. Patients received additional 200 ml gelofusine fluid challenges guided by Doppler measurements of stroke volume and corrected flow time from the investigator, in addition to any fluid given by the clinician. . Duration of surgery. Concurrent medication/care: Intraoperatively, all patients received i.v. crystalloid (Hartmann's solution), colloid in the form of gelofusine, or blood to replace estimated and measured fluid losses, in an attempt to maintain heart rate and arterial pressure within 20% of pre-induction baseline levels. . Indirectness: No indirectness. (n=31) Intervention 2: Conventional clinical assessment. Patients received additional 200 ml gelofusine fluid challenges guided by the response of the central venous pressure to a fluid challenge from the investigator, in addition to any fluid given by the clinician. . Duration of surgery. Concurrent medication/care: Intraoperatively, all patients received i.v. crystalloid (Hartmann's solution),colloid in the form of gelofusine, or blood to replace estimated and measured fluid losses, in an attempt to maintain heart rate and arterial pressure within 20% of pre-induction baseline levels. . Indirectness: No indirectness (n=29) Intervention 3: Conventional clinical assessment. Clinicians were able to give i.v. fluid as they thought appropriate. Although central venous pressure was monitored and recorded by the investigator, the clinician was unaware of these measurements and so was unable to use them to guide therapy. The investigator gave no additional fluids in this group. . Duration of surgery. Concurrent medication/care: Intraoperatively, all patients received i.v. crystalloid (Hartmann's solution),colloid in the form of gelofusine, or blood to replace estimated and measured fluid

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Study	Venn 2002[100]
	losses, in an attempt to maintain heart rate and arterial pressure within 20% of pre-induction baseline levels.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 8 days; Group 1: 3/30, Group 2: 2/29
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: Perioperative complications
- Actual outcome: Morbidity at 8 days; Group 1: 11/30, Group 2: 21/31
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 NA; Group 1: mean 13.5 days (SD 6.96); n=30, Group 2: mean 17.5 days (SD 9.46); n=29
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 ;

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 8 days; Group 1: 3/30, Group 2: 2/29
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: Perioperative complications
- Actual outcome: Morbidity at 8 days; Group 1: 11/30, Group 2: 10/29
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 ;

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Study	Venn 2002[100]
Protocol outcome 3: Length of hospital stay - Actual outcome: Length of hospital stay at NA; Group 1: mean 13.5 days (SD 6.96); n=30, Group 2: mean 17.5 days (SD 9.46); n=29 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 ; Length of stay in intensive care unit ; Hospital readmission

Study	Wakeling 2005[101]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=128)
Countries and setting	Conducted in United Kingdom; Setting: Single centre; colorectal surgery; elective
Line of therapy	Not applicable
Duration of study	Intervention time: Duration of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients requiring elective or semi-elective large bowel surgery.
Exclusion criteria	Age under 18 yr, hepatic pathology, perforated viscus, oesophageal pathology, and coagulopathy. Written, informed consent was obtained from all patients by the research nurse before participation in the study, which was approved by the local research ethics committee.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (IQR): 69.4 (11.2). Gender (M:F): 72/56. Ethnicity: Not reported
Further population details	1. Age: >60 years (69.4 (11.2)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (Median: 2). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (large bowel surgery).
Indirectness of population	No indirectness
Interventions	(n=67) Intervention 1: Non-invasive cardiac output monitoring - oesophageal doppler monitor. in addition to the routine fluid management, the patients received 250 ml boluses of colloid solution, Haemaccel (Hoechst

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Study	Wakeling 2005[101]
	Marion Roussel, Uxbridge, UK) or Gelofusine (Braun, Sheffield, UK). If the stroke volume increased by 10% or more but the CVP did not rise by 3 mm Hg or more, the fluid challenge was repeated. The fluid challenges of 250 ml were repeated until the stroke volume failed to rise by 10% and/or the CVP rose by 3 mm Hg or more. No further colloid fluid boluses were given until a 10% decrease in stroke volume occurred.. Duration of surgery. Concurrent medication/care: Patients were intubated and ventilated to normocapnia throughout the operation. Standard monitoring included ECG, pulse oximetry, capnography, and non-invasive arterial pressure. After induction of anaesthesia, a central venous line was inserted for monitoring of central venous pressure (CVP) and vascular access. Patients followed a common recovery pathway during the postoperative recovery phase.. Indirectness: No indirectness (n=67) Intervention 2: Conventional clinical assessment. Patients were managed using routine cardiovascular monitoring and CVP measurements. The CVP was used to guide i.v. fluid administration and was kept between 12 and 15 mm Hg. The anaesthetist was blinded to the oesophageal Doppler measurements made by the research assistant in this group. Duration of surgery. Concurrent medication/care: Patients were intubated and ventilated to normocapnia throughout the operation. Standard monitoring included ECG, pulse oximetry, capnography, and non-invasive arterial pressure. After induction of anaesthesia, a central venous line was inserted for monitoring of central venous pressure (CVP) and vascular access. Patients followed a common recovery pathway during the postoperative recovery phase. Indirectness: No indirectness
Funding	Academic or government funding (NHS Executive South East Research and Development grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Quality of life
- Actual outcome: Quality of life (EORTC QLQ C-30 & QLQ CR38) at 6 weeks; The EORTC QLQ C-30 and QLQ CR38 quality of life questionnaires completed 4–6 weeks after surgery showed no differences between the groups.;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: The surgical teams, nursing staff and patients themselves were blinded.; Group 1 Number missing: 3, Reason: Did not receive allocated intervention (3); Group 2 Number missing: 3, Reason: Did not receive allocated intervention (3)

Protocol outcome 2: Perioperative complications
- Actual outcome: Patients with complications at Not reported (possibly 7 days); Group 1: 24/64, Group 2: 38/64
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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Study	Wakeling 2005[101]
- Low; Indirectness of outcome: No indirectness ; Blinding details: The surgical teams, nursing staff and patients themselves were blinded.; Group 1 Number missing: 3, Reason: Did not receive allocated intervention (3); Group 2 Number missing: 3, Reason: Did not receive allocated intervention (3) Protocol outcome 3: Length of hospital stay - Actual outcome: Post-operative length of stay ; p: 0.031, Comments: Median (IQR) ODM: 10 (5.75); Conventional care: 11.5 (4.75)); 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: The surgical teams, nursing staff and patients themselves were blinded.; Group 1 Number missing: 3, Reason: Did not receive allocated intervention (3); Group 2 Number missing: 3, Reason: Did not receive allocated intervention (3)	
Protocol outcomes not reported by the study	Mortality ; Length of stay in intensive care unit ; Hospital readmission

Study	Zakhaleva 2013[108]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=91)
Countries and setting	Conducted in United Kingdom; Setting: Single centre of UK hospital.
Line of therapy	Not applicable
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 over 18 years of age presenting for bowel resection, defined as open or laparoscopic with primary anastomosis.
Exclusion criteria	Admission as an emergency case, recent oesophageal or upper airway surgery, aortic disease, or congestive heart failure.
Recruitment/selection of patients	Recruited from patients presenting within hospital.
Age, gender and ethnicity	Age - Mean (range): 57 (22-80). Gender (M:F): 40/30. Ethnicity:
Further population details	1. Age: <60 years (57 (22-80)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 2: 14; ASA 3: 58). 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: (bowel resection).

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Study	Zakhaleva 2013[108]
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Non-invasive cardiac output monitoring - oesophageal doppler monitor. Naso-oesophageal Doppler (CardioQ) placed by anesthesiologist, received intraoperative water and electrolyte according to a predetermined algorithm which incorporated the variables of cardiac output, SV and systemic vascular resistance. Duration of surgery. Concurrent medication/care: An enhanced recovery protocol was used consisting of pre-operative epidural catheter insertion, early extubation, ambulation on post-op day 0, early nutritional reintroduction. . Indirectness: No indirectness (n=40) Intervention 2: Conventional clinical assessment. Preoperative crystalloid loading at 2 ml/kg/h of fasting, and given infusion of crystalloid in volume of three to four times the actual blood loss. Additional crystalloid was given at 4-8ml/kg/h based on estimated insensible loss.. Duration of surgery. Concurrent medication/care: An enhanced recovery protocol was used consisting of pre-operative epidural catheter insertion, early extubation, ambulation on post-op day 0, early nutritional reintroduction. . Indirectness: No indirectness
Funding	Study funded by industry (Education grant from Deltex Medical)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OESOPHAGEAL DOPPLER MONITOR versus CONVENTIONAL CLINICAL ASSESSMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 30 days; Group 1: 0/32, Group 2: 0/40
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: Perioperative complications
- Actual outcome: Overall complications at 30 days; Group 1: 7/32, Group 2: 19/40
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 ; Median (range)
OD: 6 (3-30); conventional care: 5 (3-16);
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

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Study	Zakhaleva 2013[108]
Protocol outcomes not reported by the study	Quality of life ; Length of stay in intensive care unit ; Hospital readmission

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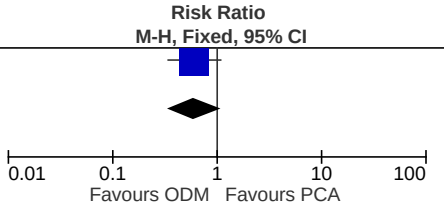
Appendix E: Forest plots

E.1 Oesophageal Doppler compared to pulse contour analysis

Figure 2: Patients with complications

Study or Subgroup	ODM Events	ODM Total	PCA Events	PCA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Feldheider 2015	6	11	9	10	100.0%	0.61 [0.34, 1.08]
Total (95% CI)		**11**		**10**	**100.0%**	**0.61 [0.34, 1.08]**
Total events	6		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.70 (P = 0.09)



E.2 Cardiac output monitoring compared to conventional assessment

Figure 3: Mortality

Study or Subgroup	Cardiac output monitoring Events	Cardiac output monitoring Total	Conventional care Events	Conventional care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Correa-Gallego 2015	2	69	0	66	1.6%	4.79 [0.23, 97.85]
Dhawan 2018	0	38	1	39	4.7%	0.34 [0.01, 8.14]
Kapoor 2015	2	60	6	60	18.9%	0.33 [0.07, 1.59]
Lai 2015	3	109	3	111	9.4%	1.02 [0.21, 4.94]
Mayer 2010	2	30	2	30	6.3%	1.00 [0.15, 6.64]
Noblett 2006	0	51	1	52	4.7%	0.34 [0.01, 8.15]
Pearse 2014	12	366	11	364	34.8%	1.08 [0.48, 2.43]
Ratti 2016	0	45	0	45		Not estimable
Senagore 2009	0	21	0	22		Not estimable
Stens 2017	1	81	1	94	2.9%	1.16 [0.07, 18.26]
Venn 2002	3	30	8	60	16.8%	0.75 [0.21, 2.62]
Zakhaleva 2013	0	32	0	40		Not estimable
Total (95% CI)		**932**		**983**	**100.0%**	**0.87 [0.53, 1.43]**
Total events	25		33			

Heterogeneity: Chi² = 3.79, df = 8 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)

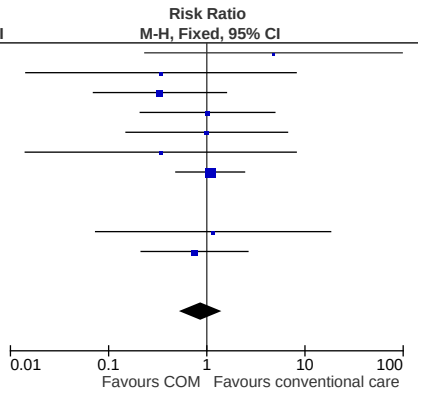


Figure 4: Patients with complications

Study or Subgroup	Cardiac output monitoring Events	Cardiac output monitoring Total	Conventional care Events	Conventional care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bartha 2013	27	70	34	72	8.8%	0.82 [0.56, 1.20]
Correa-Gallego 2015	6	69	4	66	1.1%	1.43 [0.42, 4.86]
Dhawan 2018	2	38	8	39	2.1%	0.26 [0.06, 1.13]
Mayer 2010	6	30	15	30	3.9%	0.40 [0.18, 0.89]
Moppett 2016	27	51	37	63	8.7%	0.90 [0.65, 1.26]
Noblett 2006	12	51	19	52	4.9%	0.64 [0.35, 1.19]
Pearse 2014	134	366	158	364	41.6%	0.84 [0.71, 1.01]
Ratti 2016	4	45	5	45	1.3%	0.80 [0.23, 2.79]
Salzwedel 2013	21	79	36	81	9.3%	0.60 [0.39, 0.93]
Smetkin 2009	1	20	4	20	1.1%	0.25 [0.03, 2.05]
Srinivasa 2013	26	37	27	37	7.1%	0.96 [0.72, 1.28]
Wakeling 2005	24	64	38	64	10.0%	0.63 [0.43, 0.92]
Total (95% CI)		**920**		**933**	**100.0%**	**0.77 [0.69, 0.87]**
Total events	290		385			

Heterogeneity: Chi² = 13.73, df = 11 (P = 0.25); I² = 20%
Test for overall effect: Z = 4.38 (P < 0.0001)

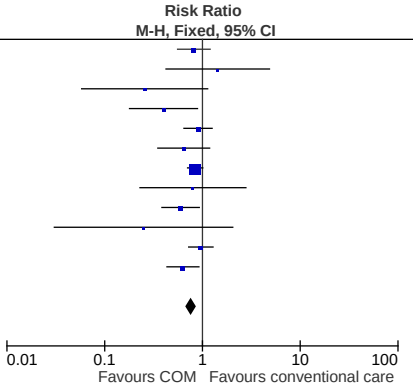


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Figure 5: Total number of complications

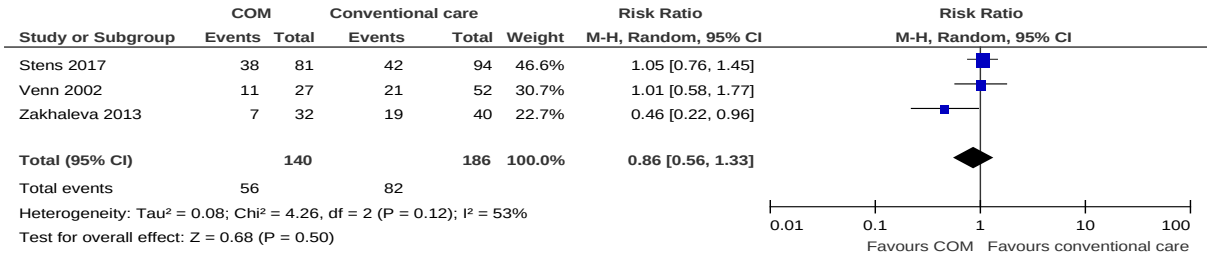

Figure 6: Patients with complications (POMS ≥1 (3-days))

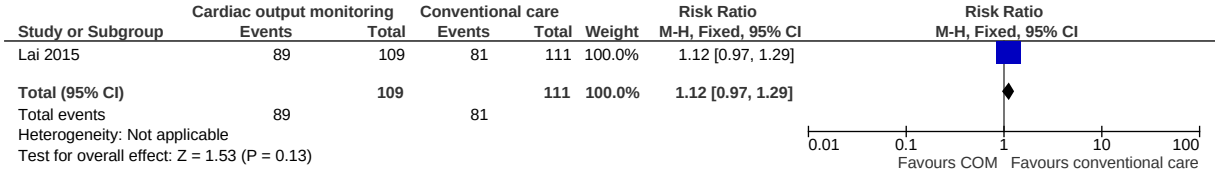

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Figure 7: Patients with complications (POMS ≥1 (5-days))

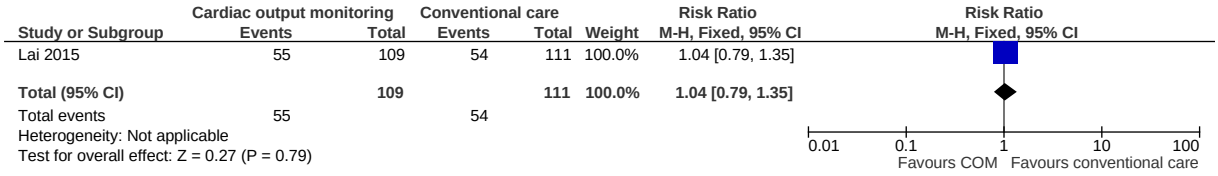

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Figure 8: Patients with complications (POMS ≥1 (8-days))

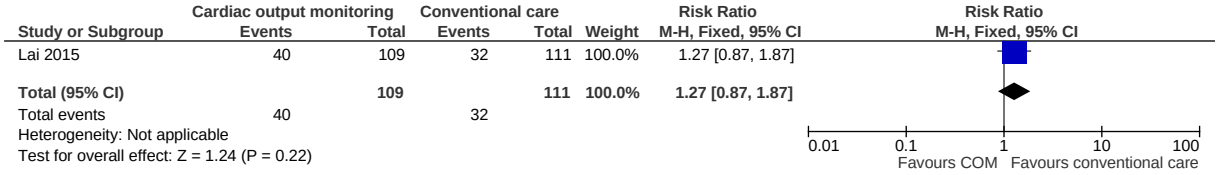

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Figure 9: Length of hospital stay

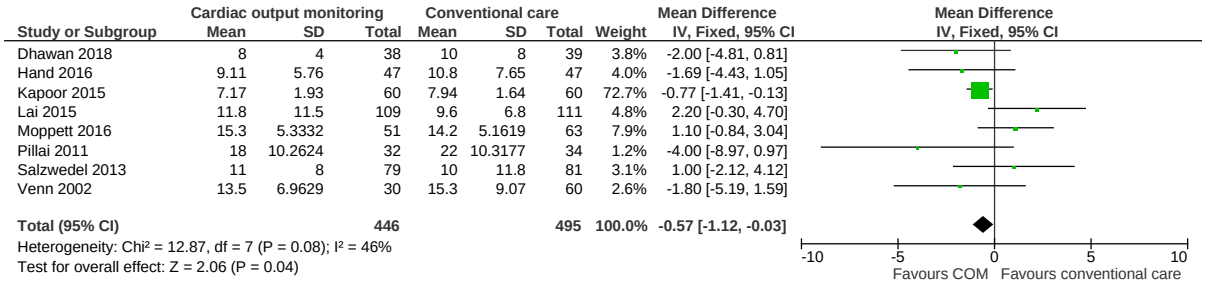

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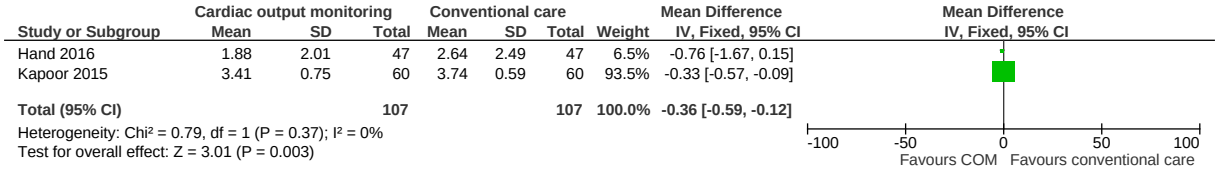
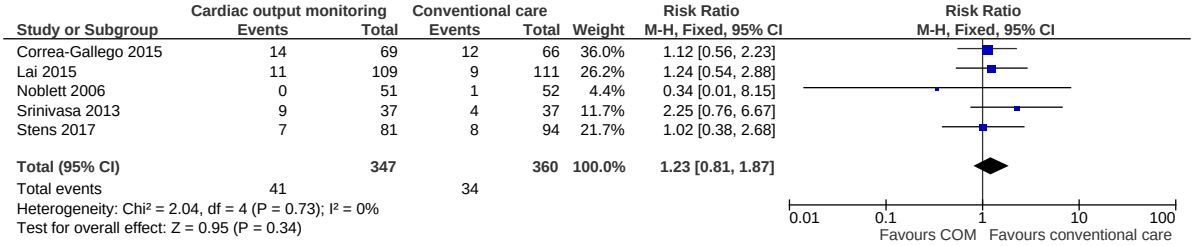
Figure 10: Length of stay in ICU



1

Figure 11: Hospital readmission



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Appendix F:GRADE tables

Table 17: Clinical evidence profile: Oesophageal Doppler monitoring versus pulse contour analysis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oesophageal Doppler	Pulse contour analysis	Relative (95% CI)	Absolute		
Patients with complications (follow-up 8 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	6/11 (54.5%)	90%	RR 0.61 (0.34 to 1.08)	351 fewer per 1000 (from 594 fewer to 72 more)	⊕⊕⊕O MODERATE	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 18: Clinical evidence profile: Cardiac output monitoring versus conventional clinical assessment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-invasive cardiac output monitoring	Conventional clinical assessment	Relative (95% CI)	Absolute		
Mortality (follow-up <90 days)												
12	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	25/932 (2.7%)	2.3%	RR 0.87 (0.53 to 1.44)	3 fewer per 1000 (from 11 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Patients with complications (follow-up <45 days)												
12	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	290/920 (31.5%)	44.4%	RR 0.77 (0.69 to 0.87)	102 fewer per 1000 (from 58 fewer to 138 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Complications (follow-up ≤30 days)												
3	randomised trials	no serious risk of	serious inconsistency[2]	no serious indirectness	Very serious[1]	none	56/140 (40%)	44%	RR 0.86 (0.56 to 1.33)	62 fewer per 1000 (from 194 fewer	⊕OOO VERY LOW	CRITICAL

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		bias								to 146 more)		
Complications: POMS ≥1 (3-days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	89/109 (81.7%)	73%	RR 1.12 (0.97 to 1.29)	88 more per 1000 (from 22 fewer to 212 more)	⊕⊕⊕O MODERATE	CRITICAL
Complications: POMS ≥1 (5-days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	55/109 (50.5%)	48.7%	RR 1.04 (0.79 to 1.35)	19 more per 1000 (from 102 fewer to 170 more)	⊕⊕⊕O MODERATE	CRITICAL
Complications: POMS ≥1 (8-days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40/109 (36.7%)	28.8%	RR 1.27 (0.87 to 1.87)	78 more per 1000 (from 37 fewer to 251 more)	⊕⊕⊕O MODERATE	CRITICAL
Length of hospital stay (Better indicated by lower values)												
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	446	495	-	MD 0.57 lower (1.12 lower to 0.03 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Length of stay in ICU (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	107	107	-	MD 0.36 lower (0.59 to 0.12 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Readmission rate (follow-up 30-60 days)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	41/347 (11.8%)	9.5%	RR 1.23 (0.81 to 1.87)	22 more per 1000 (from 18 fewer to 83 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p=0.05, unexplained by subgroup analysis.

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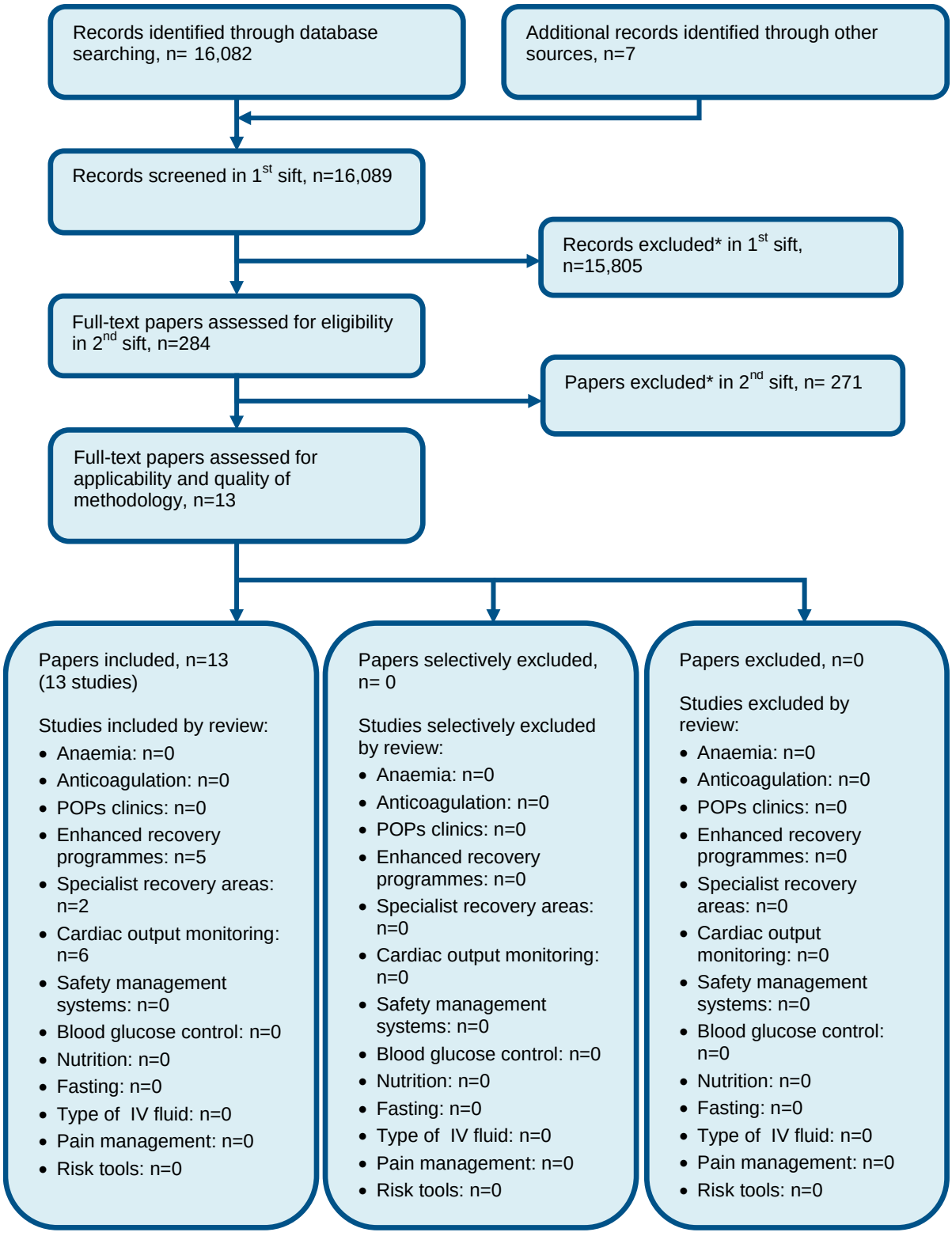
Appendix G: Health economic evidence selection

Figure 12: Flow chart of health economic study selection for the guideline



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

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Appendix H: Health economic evidence tables

Study	Bartha 2012[5]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** A short-term decision tree to model different haemodynamic fluid strategies which can result in experiencing no complications, cardiovascular compilations, other complications or death. Those alive enter a long-term Markov model to be modelled for 5 years. The possible health states in the Markov model include post cardiac complications, post stroke, post other complications, recovery after complications and	**Population:** Adults over 80 years old with hip fracture **Cohort settings:** Start age: 80 years Male: NR **Intervention 1:** Standard care (routine fluid treatment) **Intervention 2:** Cardiac output monitoring	**Total costs (mean per patient):** Intervention 1: £13,325 Intervention 2: £11,889 Incremental (2−1): -£1,436 (95% CI: -£2,321, £182; p=NR) **Currency & cost year:** 2012 Swedish Krona (presented here as 2012 UK pounds[(b)]) **Cost components incorporated:** Monitor costs (LiDCO rapid), hospital costs, costs of various complications in hospital, costs of long-term medical care costs after stroke and cardiovascular complications and death.	**QALYs (mean per patient):** Intervention 1: 2.587 Intervention 2: 2.931 Incremental (2−1): 0.344 (95% CI: 0.082, 0.492; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 is dominant[(e)] 96.4% of simulations resulted in cardiac output monitoring being dominant. **Analysis of uncertainty:** A wide range of sensitivity analyses around baseline risks, relative risks, costs, utilities and other inputs were undertaken. The dominance of cardiac output monitoring was maintained in most sensitivity analyses. Results were sensitive to relative risks for mortality and morbidity. When clinical effect was reduced by increasing the relative risk by 90% the ICER was £292 per QALY gained.

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no complications. **Perspective:** Swedish healthcare perspective **Time horizon:** 5 years **Treatment effect duration:**(a) hospital admission **Discounting:** Costs: 3%; Outcomes: 3%				
Data sources				
Health outcomes: Baseline probabilities for the decision tree were obtained from a Swedish trial of 402 participants with hip fractures. The mortality treatment effect was obtained from a meta-analysis of various trials using the same cardiac output monitor but a mixed population that was not relevant to the population in this analysis. The morbidity treatment effects were obtained from Venn 2002 which was a randomised controlled trial of adults with hip fractures but used a different cardiac output monitor. The probability of death used in the Markov model was obtained from the Swedish National Registry on Secondary Prevention in Cardiac Intensive care and the Swedish National Stroke Registry. **Quality-of-life weights:** Utilities from published literature; tariff unclear, population collected in unclear. **Cost sources:** Costs were obtained from the Swedish National Board of Health and Welfare for patients who received hip fracture surgery in 2007.				
Comments				
Source of funding: NR. **Limitations:** UK NHS perspective, costs from 2006/07 and changes in practice mean that it may not be relevant to current practice. Did not state whether discounting was used in 5 year analysis. Utilities were not from the relevant population as it was obtained from ICU survivors instead of surgery survivors. Time horizon may be too short to fully capture costs and outcomes. Baseline probabilities and treatment effects for complications were based on a single RCT therefore the treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review).				
Overall applicability:(c) Partially applicable **Overall quality:**(d) Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2012 purchasing power parities[68]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

(e) Interventions are dominant when they are both less costly and more effective.

Study	**NICE 2011[63]**

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Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: Cost comparison **Approach to analysis:** Decision tree approach with no health related quality of life and no health states. Treatment effects are included in the model as reduction in length of stay. **Perspective:** UK NHS **Time horizon:** length of hospital stay (until discharged) **Discounting:** n/a	**Population:** patients undergoing moderate and major risk surgery and high risk patients undergoing any surgery **Intervention 1:** CCA **Intervention 2:** CVP & CCA **Intervention 3:** PCA[(a)] & CCA **Intervention 4:** CVP & ODM & CCA **Intervention 5:** CVP & PCA[(a)] & CCA **Intervention 6:** ODM & CCA	**Total costs (mean per patient):** Incremental (6−1): -£966 (95% CI: NR; p=NR) Incremental (6−2): -£1,088 (95% CI: NR; p=NR) Incremental (6−3): -£1,150 (95% CI: NR; p=NR) Incremental (6−4): -£55 (95% CI: NR; p=NR) Incremental (6−5): -£1,091 (95% CI: NR; p=NR) **Currency & cost year:** 2008/09 UK pounds **Cost components incorporated:** Length of hospital stay (ICU, HDU and general ward), device costs, maintenance and consumables, fluids and staffing	None	ODM & CCA was cost saving **Analysis of uncertainty:** Deterministic analysis: different scenarios to explore different assumptions and threshold analysis carried out on all treatment effects. Increasing the effectiveness of general ward length of stay for CVP & CCA and keeping the effectiveness of ODM constant resulted in ODM no longer being cost-saving. However, there was no clinical evidence to support this scenario. PSA demonstrated that ODM was cost-saving in comparison to CVP & CCA with a saving of £1,378.

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Data sources
Health outcomes: Meta-analyses of previously conducted RCTs and Hospital Episode Statistics were used to make assumptions on the estimates in baseline reduction in hospital length of stay and ICU stay. Treatment effect was also based on assumptions that were based on RCTs, Hospital Episode Statistics and Deltex Medical audit database. **Cost sources:** Unit costs were obtained from NHS Reference Costs and PSSRU. Device costs were obtained from manufacturer's and also based on assumptions.
Comments
Source of funding: Deltex Medical **Limitations:** UK NHS perspective, costs from 2008/09 and changes in practice mean that it may not be as relevant to current practice. Measure of effect is not in line with NICE reference case methods as the analysis does not measure QALYs. Time horizon is too short and may not fully capture differences in costs and health outcomes. Some of the health benefits have not been captured and some of the treatment effects were based on assumptions. The treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review). Five out of eleven of the RCTs included in the meta-analysis used starch boluses and were excluded from the NGC clinical review. Funded by Deltex Medical.
Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: CC = cost–comparison; CCA = conventional clinical assessment; 95% CI = 95% confidence interval; CVP = central venous pressure; NR = not reported; ODM = oesophageal Doppler monitor; PPWA = pulse pressure waveform analysis; PSA = probabilistic sensitivity analysis; RCT = randomised controlled trial

(a) Note: Pulse contour analysis was used as the name of the intervention throughout the review instead of pulse pressure waveform analysis to be in line with the clinical review.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Sadique 2015**[83]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Within-trial analysis with modelled post-trial extrapolation **Approach to analysis:** Within-trial analysis of the OPTMISE RCT which had a follow-up time of 6 months. Effects were extrapolated	**Population:** Adults 50 years and over undergoing major gastrointestinal surgery Mean age: 72.2 Male:62.7% **Intervention 1:**	**Lifetime total costs (mean per patient):** Intervention 1: £8,974 Intervention 2: £8,574 Incremental (2−1): -£404 (95% CI:-£1,313, £504; p=NR) **Six month total costs (mean per patient):**	**Lifetime QALYs (mean per patient):** Intervention 1: 7.10 Intervention 2: 7.59 Incremental (2−1): 0.19 (95% CI: -0.17, 0.54; p=NR) **Six month QALYs (mean per patient):**	Intervention 2 was dominant[(d)] (cheaper and more effective) Probability Intervention 2 cost effective (£20K/30K threshold): 87%/NR **Analysis of uncertainty:** Different scenario analyses were conducted, which did not affect the results.

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beyond the trial with life expectancy after 6 being that of the age and gender adjusted general population mortality. Quality of life difference after 6 months was assumed to decline to zero after 2 years. **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 6 months, the model used survival estimates for the general population beyond this point. **Discounting:** Outcomes: 3.5%	Standard care **Intervention 2:** Cardiac output-guided haemodynamic therapy (LiDCO rapid-pulse contour analysis)	Intervention 1: £8,974 Intervention 2: £8,574 Incremental (2−1): -£404 (95% CI:-£1,313, £505; p=NR) **Currency & cost year:** 2012/13 UK pounds **Cost components incorporated:** Surgical costs, length of stay in critical care and surgical ward, blood products and device costs	Intervention 1: 0.36 Intervention 2: 0.37 Incremental (2−1): 0.01 (95% CI: 0.00, 0.02; p=NR)	Pre-specified subgroup analyses were undertaken on various patient factors such as urgency of surgery, surgical procedure category, and timing of patient recruitment. The only subgroup for which the intervention was not dominant was the early recruitment group for which the intervention was dominated.
Data sources				
Health outcomes: Results from the OPTIMISE trial informed the 6 month analysis and bivariate regression methods were used to correlate between costs and QALYs to report mean incremental costs and QALYs in the intervention group compared to control. Survival was calculated from the 6 month trial. Resource use was collected from the trial. Post-trial survival was predicted by fitting survival curves to the 6 month trial excess death rates compared to age-gender-matched UK general population life expectancy obtained from the Office for National Statistics. Different parametric specifications were applied to the trial data and all models tended to predict lower mortality up to year 2, and higher mortality after. As this was considered implausible, age-gender matched population general death rates after 6 months were used. In sensitivity analysis the Weibull function was applied. **Quality-of-life weights:** EQ-5D UK tariff. The 30 day QoL from the trial was used as the baseline QoL in the analysis. In the lifetime extrapolation, the mean value at 6 months for patients aged 72 was used, and mean QoL between year 1 and 2 was predicted linearly, so that after 2 years the mean value for trial patients was similar to that of the age matched general population. Hence QoL difference after 6 months was assumed to decline to zero after 2 years. **Cost sources:** Unit costs were obtained from NHS payment by results tariff, NHS Blood and Transplant, and British National Formulary. Device costs were obtained from manufacturers. To avoid double counting associated with cost of hospital stay, the costs of average length of stay and of 1 day in post anaesthetic recovery unit were subtracted from the national average unit cost for each eligible procedure.				
Comments				
Source of funding: NR. **Limitations:** UK NHS perspective and costs from 2012/13 may not reflect current practice. Study is based on one type of surgery and not the whole surgical population. Unclear if costs are discounted. Baseline and treatment effects are based on a single RCT therefore the treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review). The analysis did not include complications as a health outcome. Cost source slightly unclear and costing methods to avoid double counting could impact results.				
Overall applicability:[(b)] Partially applicable		**Overall quality:**[(c)] Potentially serious limitations		

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Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); NR= not reported; QALYs= quality-adjusted life years; QoL= quality of life; RCT= randomised controlled trial

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

(d) Interventions are dominant when they are both less costly and more effective.

Study	**Legrand 2015[47]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcomes: major complication avoided and death avoided) **Approach to analysis:** Decision tree with three interventions including ODM & CCA, PCA & CCA, and CCA alone. Following each intervention there were three potential outcomes: death, major complications, and no death or major complication. **Perspective:** French public health insurance. **Follow-up:** until discharged from hospital **Discounting:** N/A	**Population:** Adults undergoing intermediate and high risk abdominal surgery. **Patient characteristics:** Mean age: NR Male: NR **Intervention 1:** CCA **Intervention 2:** PCA[(a)] & CCA **Intervention 3:** ODM & CCA	**Total costs (mean per patient):** Incremental (2−1): -£334 (95% CI: NR; p=NR) Incremental (3-1): -£134 (95% CI: NR; p=NR) Incremental (3-2): £200 (95% CI: NR; p=NR) **Currency & cost year:** 2011 French euros(presented here as 2011 UK pounds[(b)]) **Cost components incorporated:** Medical devices (CardioQ-ODM and Vigileo/FloTrac), hospital costs such as procedures performed, length of stay and level of severity (comorbidities and	**Major complication avoided:** Incremental (2−1): 0.129 (95% CI: NR; p=NR) Incremental (3−1): 0.072 (95% CI: NR; p=NR) Incremental (3−2): -0.057 (95% CI: NR; p=NR) **Death avoided:** Incremental (2−1): 0.018 (95% CI: NR; p=NR) Incremental (3−1): 0.021 (95% CI: NR; p=NR) Incremental (3−2): 0.003 (95% CI: NR; p=NR)	Both PPWA and ODM were dominant[(e)] when they were compared to CCA alone, resulting in lower costs and greater health effects for major complication avoided and death avoided. ODM was dominated by PPWA for major complication avoided, and for death avoided it resulted in an ICER of £66,799 per death avoided. **Analysis of uncertainty:** PSA was conducted by performing 1000 iterations. this demonstrated that ODM and PPWA were dominant compared to CCA with most of the iterations falling in the south-east quadrant, showing it was more effective and less costly. There was uncertainty around which of the two forms of cardiac output monitoring was more cost-effective. For mortality avoided PPWA and ODM were dominant compared with CCA in 92.9% and 69.5% of cases, respectively. ODM compared with PPWA was dominant in 20.8% and was dominated in 27.6% of cases.

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		complications).		For major complications avoided PPWA and ODM were dominant compared with CCA in 97.3% and 76.1% of cases, respectively. ODM compared with PPWA was dominant in only 23.8% of cases and was dominated in 71.6% of cases. One-way sensitivity analysis showed that the results were sensitive to variations in the probabilities of death and complications, but not costs.

Data sources

Health outcomes: Baseline event data was taken from pooled data from the 13 RCTs identified in the clinical review. Relative treatment effect was obtained from the relative risks in the meta-analysis. A complication was considered as major when resulting in hospitalization in the intensive care unit or revision surgery, reported as grade 3 or 4 complications in Dindo et al.'s classification. **Cost sources:** Only considered direct medical costs of hospital costs and equipment. Hospital costs were obtained from the French national cost study by the Technical Agency for Hospital Information, based on the national DRG system. The costs used at baseline and for sensitivity analysis were the DRG costs for colic and rectal surgeries performed in a public hospital, ranging from levels 1 to 4 based on comorbidities and complications. Because death occurs most generally after a major complication, level 3 costs were used at baseline. Device costs were obtained from manufacturers. It was assumed that the equipment would last 5 years and would be used 300 times per year. Capital costs of devices were converted to an equivalent annual cost by applying a 5% discount rate to adjust for consecutive years of usage. CCA was not costed.

Comments

Source of funding: NR. **Limitations:** French healthcare perspective and 2011 euros may not be relevant to current UK practice. Study focuses on one type of surgery and does not include all major surgery. Measure of effect is not in line with NICE reference case methods as the analysis does not measure QALYs. Time horizon may be too short to fully capture costs and outcomes. The treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review). Five out of thirteen of the RCTs included in the meta-analysis used starch boluses and were excluded from the NGC clinical review.

Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: CCA= conventional clinical assessment; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CVP= central venous pressure; ICER= incremental cost-effectiveness ratio; NR= not reported; ODM= oesophageal Doppler monitor, PCA= pulse contour analysis

(a) Note: Pulse contour analysis was used as the name of the intervention throughout the review instead of pulse pressure waveform analysis to be in line with the clinical review.

(b) Converted using 2011 purchasing power parities[68]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

(e) *Interventions are dominant when they are both less costly and more effective.*

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Study	Maeso 2011[51]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome: avoided complications and avoided mortality) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Decision tree model looking at costs and outcomes until hospital discharge. Each intervention could lead to no complications, major complications or death. Effectiveness and resource use based on a meta-analysis of 3 RCTs. Long-term results were explored in sensitivity analysis. **Perspective:** Spanish healthcare **Time horizon:** until hospital discharge (long-term results were estimated as part of a sensitivity analysis. **Treatment effect**	**Population:** Adults undergoing colorectal resection **Cohort settings:** Start age: NR Male: NR **Intervention 1:** CCA **Intervention 2:** CCA & ODM **Intervention 3:** CCA & CVP **Intervention 4:** CCA & CVP & ODM	**Total costs until discharged (mean per patient):** Intervention 1: £9,239 Intervention 2: £8,672 Intervention 3: £9,190 Intervention 4: £8,308 Incremental (4−1): -£931 (95% CI: NR; p=NR) Incremental (4−2): -£364 (95% CI: NR; p=NR) Incremental (4−3): -£882 (95% CI: NR; p=NR) **Total costs for lifetime horizon (mean per patient):** Intervention 1: £14,361 Intervention 2; £13,805 Intervention 3: £14,762 Intervention 4: £13,959 Incremental (4−1): -£402 (95% CI: NR; p=NR) Incremental (4−2): £154 (95% CI: NR; p=NR) Incremental (4−3): -£803	**Survival rate (mean per patient):** Intervention 1: 0.900 Intervention 2: 0.902 Intervention 3: 0.979 Intervention 4: 0.993 Incremental (4−1): 0.093 (95% CI: NR; p=NR) Incremental (4−2): 0.091 (95% CI: NR; p=NR) Incremental (4−3): 0.014 (95% CI: NR; p=NR) **Free of major complication rate (mean per patient):** Intervention 1: 0.900 Intervention 2: 0.902 Intervention 3: 0.979 Intervention 4: 0.993 Incremental (4−1): 0.232 (95% CI: NR; p=NR) Incremental (4−2): 0.152	In all cases CCA & CVP & ODM was dominant[(e)] for survival and major complication avoided as it was cheaper and more effective than all other interventions. For the cost-utility analysis, CCA & CVP & ODM dominated CCA and CVP and CCA alone. However, for the comparison against CCA & ODM it resulted in an ICER of £114.93 per QALY. **Analysis of uncertainty:** The probability of the interventions being cost-effective at different willingness to pay values for avoided deaths was presented. The probability of CCA & CVP & ODM being cost-effective ranges from 40% to 60% at €50,000 per death avoided. In one-way sensitivity analysis the results were sensitive to the relative risk of mortality resulting in CCA & CVP & ODM not always being the best strategy. They were also sensitive to the differences in assumed length of hospital stay due to cost.

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duration:[(a)] until discharged **Discounting:** n/a for short term analysis and did not state if discounting was applied for long term analysis		(95% CI: NR; p=NR) **Currency & cost year:** 2007 Spanish Euros (presented here as 2007 UK pounds[(b)]) **Cost components incorporated:** Device costs, surgery time, hospital stay and high dependency unit stay. Staff costs were assumed to be included in the surgery time cost.	(95% CI: NR; p=NR) Incremental (4−3): 0.115 (95% CI: NR; p=NR) **QALYs (mean per patient):** Intervention 1: 13.21 Intervention 2: 13.24 Intervention 3: 14.37 Intervention 4: 14.58 Incremental (4−1): 1.37 (95% CI: NR; p=NR) Incremental (4−2): 1.34 (95% CI: NR; p=NR) Incremental (4−3): 0.21 (95% CI: NR; p=NR)	

Data sources
Health outcomes: Three studies reported data on risk of death and two studies reported data on complications and these were used for the base case analysis. Probabilities for CCA & CVP & ODM and CCA & ODM were obtained by applying the relative risks to the CCA & CVP arm. For CCA data was obtained from one RCT. In the absence of data for CCA versus CCA & ODM, data from other high risk surgery was used. Therefore the probabilities of the interventions are based on indirect relationships from various sources. Length of hospital stay data was obtained from Wakeling 2005[101] and time spent in critical care was taken from Conway 2002[21]. It was assumed that length of hospital stay for the CCA alone arm was the same as CCA & CVP. **Quality-of-life weights:** The same QALYs were applied to all patients discharged alive, as described by de Verteuil 2007[23], and used the EQ-5D (tariff not stated). **Cost sources:** Device costs were obtained from manufacturers. The calculations assumed that the equipment would last 5 years and would be used 125 times per year. Capital costs of the EDM were converted to an equivalent annual cost applying a 3% inflation increase to adjust for consecutive years of usage. Anaesthesiology service at La Paz University Hospital provided central venous catheter costs. Resource use data obtained from published sources. Unit costs obtained from the Salud Madrid accounting system. For the cost-utility analysis additional costs were obtained from de Verteuil 2007[23], but did not give a breakdown of what they incorporated. The costs associated with patients who died were considered equivalent to those for patients with complications because the RCTs examined recorded HDU stays for patients who eventually died.
Comments
Source of funding: NR. **Limitations:** Spanish healthcare perspective and 2007 euros may not be relevant to current UK practice. Study focuses on one

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type of surgery instead of all major surgery. QALYs were only included in a sensitivity analysis. Time horizon of until discharge was too short to fully capture outcomes and costs. Did conduct a sensitivity analysis with long-term horizon but assumed that people alive would incur the same costs and QALYs. The treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review) and some of the treatment effects were obtained from other high risk surgeries where there was missing data for certain comparisons. One out of four of the RCTs included in the meta-analysis used starch boluses and was excluded from the NGC clinical review.

Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: CCA= conventional clinical assessment; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; CVP= central venous pressure; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; ODM= oesophageal Doppler monitor, QALYs= quality-adjusted life years; RCT= randomised controlled trial

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2007 purchasing power parities[68]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

(e) Interventions are dominant when they are both less costly and more effective.

Study	**Mowatt 2009[60]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Meta-analysis was conducted looking at mortality and length of stay. Best and worst case scenarios were undertaken assuming: different resource use associated with length of stay, and different survival assumptions for additional	**Population:** High risk surgical adults **Cohort settings:** Start age: NR Male: NR Two pairwise comparisons are made: **Intervention 1:** CVP & CCA **Intervention 2:** ODM & CVP & CCA	**Total costs (mean per patient):** NR **Currency & cost year:** 2006/07 UK pounds **Cost components incorporated:** Costs of ODM monitor (CardioQ-ODM and CardioQ-ODM +), hospital stay and ICU stay. Costs of comparators were not included as all received conventional clinical	**QALYs (mean per patient):** NR	**ODM & CVP & CCA versus CVP & CCA:** Study concluded that ODM strategy is cost-effective at a threshold of £30,000 per QALY. The extra cost per additional survivor that would need to be incurred before ODM would no long be considered cost-effective is £4,441 (best case scenario) and £642 (worst case scenario). **ODM & CCA versus CCA:** Study concluded that ODM strategy is cost-effective at a threshold of £30,000 per QALY. The extra cost per additional survivor that would need to be incurred before ODM

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survivors from ODM. **Perspective:** UK NHS **Time horizon:** 5 years **Treatment effect duration:**[(a)] until discharged **Discounting:** NR	And: **Intervention 3:** CCA **Intervention 4:** ODM & CCA	assessment.		would no long be considered cost-effective is £11,588 (best case scenario) and £1,879(worst case scenario). **Analysis of uncertainty:** Probabilistic sensitivity analysis was conducted by performing 1000 iterations. The probability of ODM being cost-effective was not reported however most of the iterations fall in the south-east quadrant for both of the ODM & CVP & CCA versus CVP & CCA and ODM & CCA versus CCA comparisons. Therefore both ODM strategies are more effective and less costly.
Data sources				
Health outcomes: Baseline event data and relative treatment effect was taken from meta-analysis of RCTs identified in the clinical review. Assumption was made that mean length of survival per additional survivor was taken to be 1 year for the worst-case scenario and 5 years for the best-case scenario. **Quality-of-life weights:** EQ-5D (tariff not stated), QoL score of 0.66 was used at 12 months, taken from a study on intensive care unit survivors. **Cost sources:** Scottish NHS cost data and CardioQ-ODM manufacturer. Cost attached to length of stay for the worst-case scenario was £310 per day (corresponding to the cost of a day in a general medical ward) and for the best-case scenario was £1680 per day, which corresponded to the cost of a day in an ICU.				
Comments				
Source of funding: NIHR Health Technology Assessment Programme. **Limitations:** UK NHS perspective, costs from 2006/07 and changes in practice mean that it may not be relevant to current practice. Did not state whether discounting was used in 5 year analysis. Utilities were not from the relevant population as it was obtained from ICU survivors instead of surgery survivors. Does not give a breakdown of the costs for each interventions and a breakdown of the QALYs for each intervention. Shows the probability that ODM would be considered cost-effective at a £30,000 per QALY threshold, not £20,000. Assumes that people survive on average for 5 years after surgery. The treatment effects used in the analysis do not reflect the full body of available evidence for this area (23 RCTs included in the clinical review). Five out of nine of the RCTs included in the meta-analysis used starch boluses and were excluded from the NGC clinical review.				
Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations				

Abbreviations: CCA= conventional clinical assessment; CUA= cost–utility analysis; CVP= central venous pressure; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); NR= not reported; ODM= oesophageal Doppler monitor; QALYs= quality-adjusted life years; QoL= quality of life; RCT= randomised controlled trial

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

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(c) Minor limitations / Potentially serious limitations / Very serious limitations

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 19: Studies excluded from the clinical review

Study	Exclusion reason
Abbas 2008[1]	Systematic review is not relevant to review question or unclear PICO. References screened
Bahlmann 2016[2]	Systematic review is not relevant to review question or unclear PICO
Bartha 2016[4]	Post-hoc analysis of Bartha 2013
Benes 2010[6]	Interventions including starch bolus
Benes 2014[7]	No relevant outcomes
Bisgaard 2013[8]	Interventions including starch bolus
Bisgaard 2013[9]	Interventions including starch bolus
Bock 2007[10]	Not in English
Bonazzi 2002[11]	Inappropriate comparison
Brandstrup 2012[12]	Interventions including starch bolus
Buhre 1999[13]	Inappropriate study design
Bundgaard-Nielsen 2013[14]	Interventions including starch bolus
Cecconi 2011[15]	Interventions including starch bolus
Challand 2012[16]	Interventions including starch bolus
Chytra 2007[17]	Interventions including starch bolus
Colantonio 2015[18]	Interventions including starch bolus
Colbert 1998[19]	No relevant outcomes
Concha 2011[20]	Not in English
Conway 2002[21]	Interventions including starch bolus
Donati 2007[25]	Inappropriate comparison
El Sharkawy 2013[26]	Interventions including starch bolus
Elgendy 2017[27]	Interventions including starch bolus
Forget 2010[29]	Interventions including starch bolus
Funk 2015[30]	Interventions including starch bolus
Gan 2002[31]	Interventions including starch bolus
Giglio 2012[32]	Systematic review is not relevant to review question or unclear PICO. References screened
Gomez-Izquierdo 2015[33]	Systematic review is not relevant to review question or unclear PICO. References screened
Gómez-Izquierdo 2017[34]	Interventions including starch bolus
Gurgel 2011[35]	Systematic review is not relevant to review question or unclear PICO. References screened
Harten 2008[37]	Interventions including starch bolus
Joyce 1990[38]	Inappropriate comparison
Kapoor 2008[39]	Incorrect interventions
Kawahito 1999[41]	Inappropriate study design
Krishnamurthy 1997[42]	Inappropriate study design
Laupland 2002[45]	Systematic review is not relevant to review question or unclear

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Study	Exclusion reason
	PICO
Lee 2015[46]	Interventions including starch bolus
Legrand 2015[47]	Systematic review is not relevant to review question or unclear PICO. References screened
Lewis 2016[48]	Systematic review is not relevant to review question or unclear PICO. References screened
Linden 2010[99]	Interventions including starch bolus
Lopes 2007[50]	Interventions including starch bolus
Maheshwari 2018[52]	Inappropriate comparison
Mayer 2009[54]	Systematic review is not relevant to review question or unclear PICO
McKendry 2004[55]	Inappropriate intervention
McKenny 2013[56]	Interventions including starch bolus
Michard 2017[57]	Systematic review is not relevant to review question or unclear PICO. References screened
Mowatt 2009[60]	Systematic review is not relevant to review question or unclear PICO. References screened
Mythen 1995[61]	Interventions including starch bolus
NCT 2010[64]	Clinical trial website with no published results
NCT 2013[65]	Clinical trial website with no published results
NCT 2017[66]	Clinical trial website with no published results
Owall 1992[69]	No relevant outcomes
Pavlovic 2016[70]	Interventions including starch bolus
Peng 2014[72]	Interventions including starch bolus
Pestana 2014[73]	Interventions including starch bolus
Phan 2014[74]	Interventions including starch bolus
Picard 2016[75]	Interventions including starch bolus
Polonen 2000[77]	Inappropriate comparison
Poso 2014[78]	Interventions including starch bolus
Ramsingh 2016[79]	Clinical trial website with no published results
Ripolles 2016[82]	Systematic review is not relevant to review question or unclear PICO. References screened
Scheeren 2013[85]	Interventions including starch bolus
Schultz 1985[86]	Inappropriate comparison
Sinclair 1997[89]	Interventions including starch bolus
Slagt 2014[90]	Systematic review is not relevant to review question or unclear PICO
Srinivasa 2011[92]	Systematic review is not relevant to review question or unclear PICO. References screened
Stewart 2009[95]	Inappropriate comparison
Sundaram 2016[96]	No relevant outcomes
Szakmany 2005[97]	Interventions including starch bolus
Valentine 1998[98]	Inappropriate comparison
Walsh 2008[102]	Systematic review is not relevant to review question or unclear PICO. References screened
Warnakulasuriya 2016[103]	Interventions including starch bolus
Wetterslev 2016[104]	Systematic review is not relevant to review question or unclear PICO. References screened

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Study	Exclusion reason
Wiles 2011[105]	Study protocol
Xu 2017[106]	Interventions including starch bolus
Yu 2015[107]	No relevant outcomes
Zeng 2014[109]	Study has since been retracted
Zhang 2012[111]	Interventions including starch bolus
Zhang 2013[110]	Interventions including starch bolus
Zheng 2013[112]	Interventions including starch bolus
Zollner 2001[113]	Inappropriate comparison

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 20: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

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