Intraoperative fluid management technologies

Technologies which enable intraoperative fluid monitoring as a component of an enhanced recovery programme

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Declarations of interests

The Cedar team has no interests to declare with respect to any individual technology referred to in this report. Cedar produced this work as part of a contract with NICE for evidence preparation and assessment services, but was solely responsible for the design of the methods and retained editorial control throughout the development and publication of the report.

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Presentational style of this report

Kent, Surrey and Sussex Academic Health Science Network advised Cedar on the presentational style of this report. Specifically the Executive Summary and also Section 5, 'RCT evidence for the technologies,' both summarise the included evidence with a focus on brevity. Further details for each individual included randomised controlled trial (RCT) are available in separate Evidence Tables, accessible via hyperlinks in Section 5 of this report. The Evidence Tables include:

- A systematic description of the study
- Numerical data for predefined outcomes
- p values
- Comments based on critical appraisal.

Abbreviations

ASA	American Society of Anesthesiologists physical status classification system
CO	Cardiac output: the volume of blood pumped by the heart in one minute
CI	Cardiac index: CO indexed to body surface area
CP/CPO	Cardiac power
CPI	Cardiac power index
CVP	Central venous pressure
DO_2	Oxygen delivery
DO_2I	Oxygen delivery index
ECG	Electrocardiogram
ERP	Enhanced recovery programme
EVLWI	Extra vascular lung water index
FT	Flow time
FTc	Flow time corrected for heart rate
GEDV	Global end diastolic volume
GEDVI	Global end diastolic volume index
GDT	Goal directed fluid therapy
Hb	Haemoglobin
HES	Hydroxyethyl starch
HR	Heart rate
IBP	Invasive blood pressure
ITBV	Intrathoracic blood volume
ITBVI	Intrathoracic blood volume index
LVEDP	Left ventricular end diastolic pressure
MAP	Mean arterial pressure
MD	Minute distance
NIBP	Non invasive blood pressure
PAC	Pulmonary artery catheter
PAOP	Pulmonary artery occlusion pressure
PPV	Pulse pressure variation
PPWA	Pulse pressure waveform analysis
PVI	Pleth variability index
$ScvO_2$	Central venous oxygen saturation
SpO_2	Peripheral oxygen saturation
SD	Stroke distance
SV	Stroke volume: the volume of blood pumped by the heart in one beat
SVI	Stroke volume indexed to body surface area
SVV	Stroke volume variation
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index: SVR indexed to body surface area

Contents

Executive summary

Background

Enhanced Recovery Programmes (ERP) aim to both standardise and improve numerous elements of perioperative care. One element of ERP is intraoperative fluid management (IOFM). The aim of IOFM is to provide the patient with the correct amount of intravenous fluid during surgery and to avoid both fluid overload (leading to complications such as lung oedema), and hypoperfusion of organs, leading to delayed surgical recovery and associated with surgical complications.

Within ERP, IOFM is driven by goal-directed fluid therapy (GDT), sometimes referred to in literature as 'individualised fluid optimisation'. In GDT, additional intraoperative monitoring technologies are used to measure haemodynamic parameters that are closely related to cardiac output. Typically GDT uses a fluid management protocol to guide the anaesthetist to give 'fluid challenges'. These are boluses of fluid given periodically until the measured parameter indicates that the patient has the optimal circulating blood volume, thus avoiding hypovolaemia and fluid overload.

This report describes the technologies currently available to the NHS, and indicated for IOFM, and summarises the evidence from published randomised trials (RCTs) for their efficacy regarding changes in hospital length of stay and post-operative complications, compared to standard care.

Points to consider when summarising the results of the RCTs

The RCTs show considerable heterogeneity in terms of surgical setting, patient sample, the sophistication of the fluid protocol(s) studied, the use of non protocol fluid and vasoactive/inotropic drugs, and the management of the control arm(s).

- There is no consistent definition of standard care in the control arms of the included RCTs. Control arm care varies in the RCTs according to the risk level of surgery and the prevailing fluid giving strategy in the setting of care (this may favour a liberal or restrictive fluid volume and may use different fluid types). Standard care has also evolved over time to become more sophisticated with the emergence of ERP. However ERP may not be applied equally across the NHS or across different surgical specialities.
- In some instances GDT is performed in the immediate postoperative period (up to 24 hours from surgery). As this too may influence acute postoperative complications, we included studies of GDT in this period; in some studies GDT is performed in both the intraoperative and postoperative periods.
- Some RCTs compare two or more fluid protocols using the same technology. These may be protocols defined by the investigators rather than the manufacturer of the technology. We considered these to be relevant studies of IOFM.
- Detailed data and comments based on critical appraisal of each study are available in evidence tables, accessible via hyperlinks in Tables 4-10.

Results

Thirteen technologies were identified. For seven technologies a total of 39 published randomised trials were found and included (Table 1). We found no randomised trials directly comparing two or more technologies when used for IOFM.

Table 1: Volume of included randomised trials using the technologies

Technology	Number of included RCTs
CardioQ-ODM	16
FloTrac	10
LiDCO*plus*	6
LiDCO*rapid*	2
PiCCO	2
Pleth variability index (PVI) on Radical 7	2
ProAQT	1

We identified six technologies that may be used for IOFM but which have not been studied in published randomised trials:

- CardioQ-ODM+
- ccNexfin
- esCCO
- ICON
- NICOM
- Uscom 1A

Further details on these six technologies are provided in Table 11, page 45.

The following sections summarise the included RCTs for each technology in alphabetical order,

Summary of RCTs using CardioQ-ODM

Intraoperative GDT – length of hospital stay

For intraoperative GDT, thirteen trials compare CardioQ-ODM guided GDT with standard care. Of these, six (Gan *et al.* 2002; Mythen & Webb 1995; Noblett *et al.* 2006; Sinclair *et al.* 1997; Venn *et al.* 2002; Wakeling *et al.* 2005) show clear benefits for CardioQ-ODM over standard care for reduced hospital stay (in one study of patients with hip fracture (Venn *et al.* 2002) this was expressed as time

to fitness for discharge). Differences in length of stay between arms range from 1.5-8 days. Six trials found no difference in length of stay between CardioQ-ODM guided GDT and standard care (Brandstrup *et al.* 2012; Challand *et al.* 2012; McKenny.M. *et al.* 2013; Pillai *et al.* 2011; Srinivasa *et al.* 2013; Zakhaleva *et al.* 2013). One trial found hospital stay to be shorter in the standard care arm than in two GDT arms, both using CardioQ-ODM (Senagore *et al.* 2009). However the differences involved were small: 7 hours and 11 hours.

Intraoperative GDT – complications

Of the thirteen trials comparing CardioQ-ODM guided GDT with standard care, six trials (Gan *et al.* 2002; Mythen & Webb 1995; Noblett *et al.* 2006; Pillai *et al.* 2011; Wakeling *et al.* 2005; Zakhaleva *et al.* 2013) favour CardioQ-ODM over standard care for reduced complications and seven found no difference or did not report complications (Brandstrup *et al.* 2012; Challand *et al.* 2012; McKenny.M. *et al.* 2013; Senagore *et al.* 2009; Sinclair *et al.* 1997; Srinivasa *et al.* 2013; Venn *et al.* 2002).

Postoperative GDT

In the immediate postoperative setting, two trials show a benefit arising from CardioQ-ODM in reduced hospital stay of 1.3-2 days compared to standard care (El Sharkawy *et al.* 2013; McKendry *et al.* 2004). Data in one study were suggestive of reduced complications from CardioQ-ODM, but with no statistical analysis (McKendry *et al.* 2004) and in the other study there was a lower rate of postoperative nausea and vomiting in the GDT arm (El Sharkawy *et al.* 2013).

Summary of RCTs using FloTrac

Intraoperative GDT

Two trials found a difference in length of hospital stay in favour of FloTrac guided GDT over standard care with a difference of between 2.5-4 days (Mayer *et al.* 2010; Ramsingh *et al.* 2013). One trial (Benes *et al.* 2010) found that FloTrac guided GDT shortened hospital stay by 1 day, but only in a per protocol analysis (not in the intention-to-treat analysis). Four trials found no difference in hospital or critical care stay between FloTrac guided GDT and standard care (Cecconi *et al.* 2011; Scheeren *et al.* 2013; Van Der Linden *et al.* 2010; Zhang *et al.* 2013).

Two trials demonstrated a clear benefit from FLoTrac guided GDT compared to standard care in reducing postoperative complications (Benes *et al.* 2010; Mayer *et al.* 2010). One trial found that wound infections were reduced in the FloTrac arm compared to standard care, but not general complications (Scheeren *et al.* 2013). One study demonstrated a lower rate of postoperative nausea/vomiting in the FloTrac group compared to standard care, but with no difference in other complications (Zhang *et al.* 2013). Another study found a lower rate of minor complications in the FloTrac arm compared to the control arm, but with no difference in major complications (Cecconi *et al.* 2011). The remaining studies (Ramsingh *et al.* 2013; Van Der Linden *et al.* 2010; Wang *et al.* 2012) found no difference in complications between groups, or provided no analysis, but one study found that bowel recovery after surgery was quicker in the GDT arm (Ramsingh *et al.* 2013).

Intra/postoperative GDT

The study by Zheng *et al.* 2013 compared FloTrac guided GDT with standard care in elderly patients undergoing gastrointestinal surgery, where GDT was continued for 24 hours postoperatively. There was no significant difference in the rate of adverse cardiac events between groups. Bowel function outcomes postoperatively favoured the FloTrac group as did the rate of nausea and vomiting. ICU stay and hospital stay were shorter in the FloTrac group (Zheng *et al.* 2013).

Postoperative GDT

One trial found no difference in length of hospital stay between FloTrac guided GDT and standard care (Kapoor *et al.* 2008). This study did not analyse complications.

Summary of RCTs using LiDCOplus

Intraoperative GDT

Three trials (Bartha *et al.* 2013; Bisgaard *et al.* 2013; Harten *et al.* 2008) did not demonstrate a clear advantage of LiDCO*plus* guided GDT over control in terms of complications and length of hospital stay, although one of these trials found LiDCO*plus* to be superior to control for complications, when analyses were adjusted for demographic/comorbidity factors, or when analysis was restricted to fluid related complications (Bisgaard *et al.* 2013). The authors of the Bartha study acknowledged that their study was underpowered to detect a difference in complications. One trial used LiDCO*plus* guided GDT in both arms and found that a restrictive fluid protocol was superior to a conventional protocol for the number of patients with complications, but not for total complications or length of stay outcomes (Lobo *et al.* 2011).

Postoperative GDT

One trial strongly favoured LiDCO*plus* over standard care in terms of a difference in length of stay of 3 days, and a reduced rate of complications following major surgery (Pearse *et al.* 2005). A second three arm trial found no differences in complication rates or length of hospital stay between LiDCO*plus* guided GDT, LiDCO*plus* guided GDT with inotrope and standard care.(Jhanji *et al.* 2010) though the authors acknowledged that their study was underpowered to detect a difference in complications.

Summary of RCTs using LiDCOrapid

Intraoperative GDT

A trial comparing two fluid protocols (crystalloid versus colloid) both guided by LiDCO*rapid* found no difference in complications or length of hospital stay between groups (Yates *et al.* 2013).

Postoperative GDT

One trial of an enhanced recovery programme in liver resection (which included LiDCO*rapid* guided GDT) found that the enhanced recovery programme reduced hospital stay by three days compared to standard care (Jones *et al.* 2013). There was no difference in complications between arms but bowel recovery outcomes favoured the enhanced recovery programme.

Summary of RCTs using PiCCO

Intraoperative GDT

The study by Lenkin *et al.* 2012 compared PiCCO guided GDT with GDT guided using a pulmonary artery catheter. There was no analysis of postoperative complications or hospital stay, but duration of respiratory support favoured the PiCCO group.

Intra/postoperative GDT

The study by Smetkin *et al.* 2009 compared PiCCO guided GDT with standard care (based on a complex fluid protocol). In each group the protocols were followed to 6 hours postoperatively. The study found no difference postoperative complications, though hospital stay was shorter in the PiCCO guided GDT group.

Summary of RCTs using Pleth Variability Index – PVI – on Masimo Radical 7

Two randomised trials were identified (Forget *et al.* 2010; Forget *et al.* 2013). Both studies compared PVI guided GDT versus standard care (which included the insertion of a central venous catheter) and found no difference between groups for complications or length of hospital stay. However, these studies were possibly underpowered to detect many of these endpoints.

Summary of RCTs using ProAQT

One randomised trial was identified (Salzwedel *et al.* 2013), which found that GDT guided by ProAQT reduced postoperative complications compared to standard care. There was no difference in hospital stay between groups.

Conclusions

- We identified seven technologies used for GDT (from five manufacturers) that have been used in randomised trials of GDT and a further six technologies that currently have not been studied in randomised trials.
- We identified no randomised studies directly comparing two or more technologies used for GDT.
- Interpretation of the effects of GDT studied in numerous randomised trials is complicated by differences in the case mix of patients, the fluid protocols used, the choice of fluids used (and the role of non protocol fluid), the role of inotropic / vasoactive drugs and the management of the control arm. The control arms of recently published studies may reflect modern enhanced recovery programmes. Such programmes aim to improve and standardise care for surgical patients by optimising in the perioperative period numerous aspects of care including: patient information, nutrition, mobility and analgesia, in addition to GDT. These may confound discerning the effects of the GDT.
- Choice of a particular technology to use for GDT in a clinical setting is likely to depend upon:
    - The strength of evidence for the efficacy and safety of the technology
    - The extent of need in the patient group for invasive monitoring: the technologies offer different levels of invasive monitoring

- Whether continuous, ‘hands off’ monitoring is required, or whether periodic measurement is sufficient for GDT
- Whether manual calibration is required: manual calibration ensures high accuracy of measurement but may be time consuming in a busy operating theatre environment (but may be easier in the critical care setting).

1 Introduction

In recent years there have been nationally coordinated efforts to improve the perioperative care of patients undergoing surgery under general or regional anaesthesia. This has led to the emergence of Enhanced Recovery Programmes (ERP), which aim to both standardise and improve numerous elements of perioperative care, such as patient education, nutrition, anaesthesia, mobilisation, pain control, intraoperative fluid management and discharge criteria (Jones *et al.* 2013).

Thus one element of ERP is intraoperative fluid management (IOFM). The aim of IOFM is to provide the patient with the correct amount of intravenous fluid during surgery and to avoid both fluid overload (leading to complications such as lung oedema), and hypoperfusion of organs, leading to delayed surgical recovery and associated with surgical complications.

The following initiatives have mandated or supported either ERP or specifically, IOFM:

- The Enhanced Recovery Partnership Programme's document titled, 'Delivering enhanced recovery – Helping patients to get better sooner after surgery' - this set out a new approach to the preoperative, intraoperative and postoperative care of patients undergoing surgery, and promoted individualised goal-directed fluid therapy (Department of Health 2010).
- Department of Health white paper 'Innovation Health and Wealth' (2011) which launched "a national drive to get Oesophageal Doppler Monitoring, or similar fluid management technology, into practice across the NHS", as one of a set of "high impact innovations" (Department of Health 2011).
- Commissioning for Quality and Innovation (CQUIN) payments, operating since April 2013, whereby service providers are incentivised to comply with the high impact innovations described above (NHS Technology Adoption Centre 2013).
- The National Institute for Health and Care Excellence (NICE) Medical Technology Guidance on CardioQ-ODM (2011), which states: "The CardioQ-ODM should be considered for use in patients undergoing major or high-risk surgery or other surgical patients in whom a clinician would consider using invasive cardiovascular monitoring".(National Institute for Health and Care Excellence 2011).
- NHS Technology Adoption Centre's Adoption Pack for Fluid Management Technologies (2013): This was commissioned by the Department of Health to help trusts implement IOFM technologies (NHS Technology Adoption Centre 2013).

Traditionally for most surgical procedures IOFM was based on the monitoring of basic physiological parameters including continuous electrocardiogram (ECG), noninvasive blood pressure (NIBP), noninvasive oxygen saturation (SpO_2), urine output and possibly central venous blood pressure (CVP). These parameters do not provide much warning of changes in the patient's fluid status.

Within ERP, IOFM is driven by goal-directed fluid therapy (GDT), sometimes referred to in literature as 'individualised fluid optimisation'. In GDT, additional intraoperative monitoring technologies are used to measure haemodynamic parameters that are closely related to cardiac output. Typically GDT uses a fluid management protocol to guide the anaesthetist to give 'fluid challenges'. These are

boluses of fluid given periodically until the measured parameter indicates that the patient has the optimal circulating blood volume, thus avoiding hypovolaemia and fluid overload.

Cardiovascular parameters may be measured using the Pulmonary Artery Catheter (PAC). This device, whilst still regarded as "the gold standard" is infrequently employed outside of cardiothoracic surgical cases or Intensive Care Units (ICUs) due to concerns over its safety and is therefore not regarded in this report as a technology for IOFM.

To date there has been no NHS-commissioned evidence review focusing on the evidence supporting each individual technology. This report describes the technologies currently available to the NHS, and indicated for IOFM, and summarises the evidence from published randomised controlled trials (RCTs) for their efficacy regarding changes in hospital length of stay and post-operative complications, compared to standard care.

This report briefly describes for each technology:

- the components
- the technical basis for how each technology works
- the fluid protocol for GDT used with the technology, where available
- the evidence for the efficacy of the technology, focusing on patient-relevant end points reported in randomised controlled trials.

2 Methods

2.1 Study eligibility criteria

The approach for reviewing the evidence is summarised in Table 2 using the PICOS framework (Centre for Reviews and Dissemination 2008) as an example:

Table 2: PICOS framework for reviewing the evidence

Population	Patients undergoing surgery and receiving goal-directed IOFM.
Intervention	Any technology marketed in the UK to assist intraoperative fluid management as part of individualised goal directed fluid therapy, excluding: • Pulmonary artery catheters: these provide an accurate measure of cardiac output but are highly invasive, carry a risk for the patient and would not be routinely used for GDT. • Transoesophagel echocardiography: these devices measure cardiac output and visualise heart structure. They are a cardiac surgery speciality and would not be routinely used for GDT.
Comparator	• Standard care: conventional clinical assessment includes as a minimum, monitoring of heart rate with continuous ECG, non-invasive blood pressure monitoring, urine output measurement by urinary catheter, and possibly cardiac preload monitoring with central venous pressure (CVP) catheter. Higher risk cases may require an arterial catheter. • Alternative fluid protocols or direct comparisons of different GDT technologies.
Outcome measures	• Rate of complications following surgery • Length of hospital stay (or length of stay in a particular setting e.g. critical care) • Indicators of recovery from surgery (e.g. for bowel surgery, time to oral diet) As intermediate outcomes or confounding factors, the following will be recorded: • Volume & type of fluid administered • Use of inotropic or vasoactive drugs
Study design	• Randomised controlled trials

2.2 Literature search for electronic databases

Three literature search strategies were designed to identify studies of technologies based on the principles of Doppler, electrical impedance and pulse pressure measurement. These three broad technology groups were identified from the NHS Technology Adoption Centre's Adoption Pack for Fluid Management Technologies (2013). The search strategies were designed for the Medline database and modified for the Embase and HMIC databases so a total of nine electronic searches were run on 5th – 6th August 2013.

Link to search strategies

2.3 Additional sources of evidence

The manufacturer (or supplier to the UK) of each technology listed in the NHS Technology Adoption Centre's Adoption Pack for Fluid Management Technologies (2013) was contacted and asked to identify relevant evidence for their own technology. The reference list of a recent key publication was utilised: a high quality systematic review which identified randomised trials of GDT published up to March 2012 and performed meta-analyses of mortality following GDT compared to standard care (Grocott *et al.* 2013). In addition we utilised a list of RCTs of GDT using any technology, and maintained by Deltex Medical, the manufacturer of CardioQ-ODM technologies. We accepted relevant RCTs sent by manufacturers if received by Cedar on or before 8th November 2013.

2.4 Data extraction and critical appraisal

An evidence table was compiled for each individual study, to document data extraction. These included wherever possible, the flow charts for relevant fluid protocols, and copyright permission to reproduce the protocols was sought. The evidence tables are available via hyperlinks from this document. Critical appraisal was performed using the NICE checklist for randomised trials. Salient comments based on critical appraisal were added to the evidence tables.

We sought randomised trials where technologies were used for GDT, reported acute postoperative complications or length of hospital stay and compared either:

- GDT versus standard care: as a minimum, standard care includes monitoring of noninvasive blood pressure (NIBP), continuous electrocardiogram (ECG), noninvasive oxygen saturation (SpO_2), urine output and possibly central venous blood pressure (CVP). However standard care can often require more invasive monitoring depending on the length and type of surgery, or the patient's own surgical risk factors.

- Two or more strategies of fluid therapy where at least one strategy was GDT e.g. GDT versus a restrictive fluid strategy, or strategies of GDT using different fluid types.

The relevant setting of care was the use of GDT in the intraoperative and immediate postoperative periods, up to 24 hours postoperatively. Acute postoperative complications included any that occurred prior to hospital discharge. For each RCT reviewed we used evidence tables to record:

- The study group and surgical setting
- The fluid management protocol(s) used for GDT in each study
- The volume of fluids administered
- Use of inotropic/vasoactive drugs
- Postoperative complications and length of hospital stay.

2.5 Review of the draft report by manufacturers

A draft report was circulated to manufacturers in November 2013 and the report was revised in the light of their comments. Broadly the changes related to:

- Correction of errors

- Technical details of the technologies, including clarification of the relationship between proprietary parameters used for GDT and compatible monitoring hardware
- Identification of additional fluid management protocols for use with the technologies
- Additional information on published trials e.g. typographical errors with p values that change outcomes, or trials in progress
- Removal of two trials of oesophageal Doppler guided GDT because they used not the CardioQ-ODM technology, but a Doppler technology made by a different manufacturer and is no longer available
- Placing greater emphasis on Section 6: Limitations.

3 The technologies explained

This section explains the technical aspects of each technology that is supported by RCT evidence, together with GDT protocols where available. Brief descriptions of technologies that are not supported by RCT evidence are provided in Table 11, page 45.

3.1 CardioQ-ODM

NICE reviewed and supports CardioQ-ODM. The NICE Medical Technology Guidance on CardioQ-ODM states: “The CardioQ-ODM should be considered for use in patients undergoing major or high-risk surgery or other surgical patients in whom a clinician would consider using invasive cardiovascular monitoring”.(National Institute for Health and Care Excellence 2011).

3.1.1 Components

CardioQ-ODM is intended for use in moderate to high risk surgical or critical care patients including those who would not otherwise warrant the risk of the insertion of a pulmonary artery catheter or arterial or CVP line. CardioQ-ODM is minimally invasive. The technology consists of a monitor and a disposable oesophageal probe. Probes are available for adults (age 16-99 years of age) and children (0-15 years of age), with versions that are designed for post-operative monitoring of awake patients with the probe placed during anaesthesia: these versions may also be placed into those awake patients who accept insertion. The oesophageal probe is inserted either orally to a depth of 35-40cm from the incisors, or nasally to a depth of 40-45cm from the nasal septum. This places the probe tip in the region of the 5^{th}-6^{th} thoracic vertebrae, where the aorta runs parallel to, and about 1cm from the oesophagus.

3.1.2 Technical basis of operation

CardioQ-ODM uses the Doppler principle whereby a transducer on the probe tip emits an ultrasound signal, which is reflected back to a second transducer on the probe tip by the moving red blood cells in the aorta. This enables measurement of the velocity of the blood in the descending thoracic aorta, and display of a velocity-time waveform on the monitor. CardioQ-ODM software uses a proprietary nomogram that converts the measured stroke distance (the distance travelled by the ejected blood each heart beat which is calculated from the blood velocity and ejection time) into

stroke volume, using an internal calibration constant based on clinician-inputted patient's age, weight and height. No other measurement or calibration is required.

Placement of the probe typically takes less than3 minutes, and the clinician is required to adjust the depth and rotational angle of the probe until the typical aortic waveform shape is observed. Due to the need to focus the signal, CardioQ-ODM is not a hands-free, continuous measurement device, and adjustment should be considered each time a reading is needed to guide fluid therapy.

CardioQ-ODM displays the following parameters:

- Cardiac output
- Stroke distance
- Stroke volume
- Heart rate
- Stroke volume index
- Flow time corrected
- Peak velocity
- Cardiac index

Other available parameters

- Mean acceleration
- Minute distance
- Flow time to peak
- Delivered oxygen
- Delivered oxygen index
- Systemic vascular resistance
- Systemic vascular resistance index

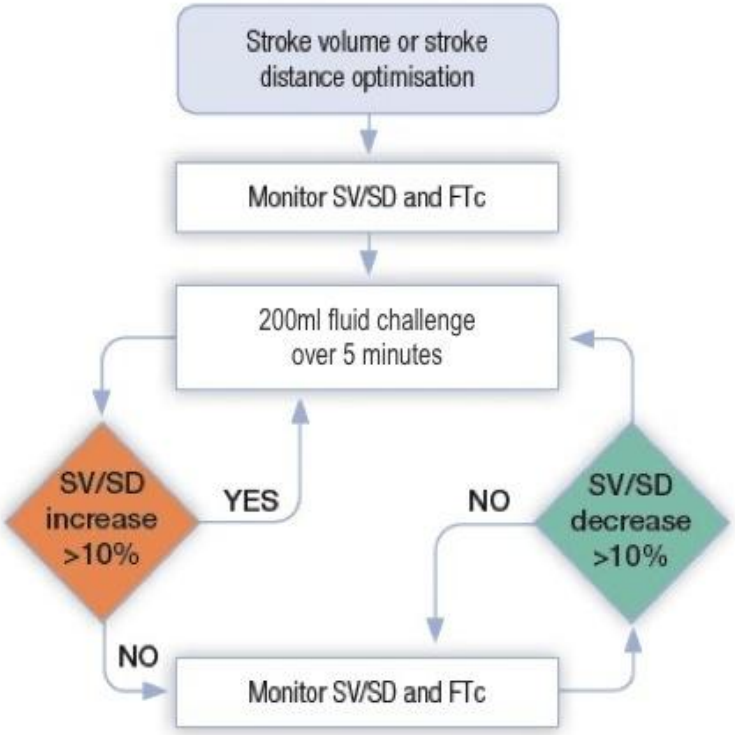
3.1.3 Contraindications or limitations on use

Caution should be applied in patients with pathology of oropharynx or oesophagus and undue force should not be applied during probe insertion. The accuracy of the cardiac output measurement may be reduced in patients undergoing epidural anaesthesia, and volumetric measurements (stroke volume and cardiac output) will not be displayed in patients with body metrics outside the nomogram range (adults: 30-150kg weight, 149-212cm height, children: 3-60kg weight, 50-170cm height). However in these patients stroke distance remains a reliable parameter. Signal acquisition is interrupted by periods of diathermy and may be affected by the use of intra-aortic balloon pumps or in patients with thoracic aortic aneurysm.

3.1.4 Fluid management protocol

Deltex Medical provide a fluid management protocol for use with CardioQ-ODM (Figure 1)

Figure 1: Fluid management protocol (reproduced with permission from Deltex Medical)



There are a number of more sophisticated versions of this protocol incorporating FTc and/or CVP: the 10% change in SD/SV is common to all ODM protocols.

3.2 FloTrac

3.2.1 Components

The FloTrac system, consists of the Vigileo monitor (or EV1000 platform) and the FloTrac sensor, which connects to an existing arterial catheter. FloTrac provides continuous haemodynamic monitoring based on arterial pressure measurement. The FloTrac sensor may be used with the EV1000 clinical platform or Vigileo monitor to continuously measure and display key flow parameters. FloTrac is intended for use in surgical and critical care patients.

3.2.2 Technical basis of operation

The FloTrac system uses an algorithm, based on measured arterial pressure, with additional variables entered by the clinician: age, gender, height, weight. From this FloTrac calculates SV, which is updated every 20 seconds.

FloTrac requires no manual calibration because the FloTrac algorithm accounts for changes in compliance and resistance (vascular tone) using a conversion factor. The factor, χ, is a multivariate polynomial equation which incorporates factors such as the standard deviation of mean arterial

pressure, skewness and kurtosis of the arterial waveform, and vascular compliance and resistance. The Flotrac algorithm calculates cardiac output as follows:

$CO = HR * [sd(BP) * \chi]$

FloTrac measures the following parameters:

- Cardiac output / cardiac index
- Stroke volume / stroke volume index
- Systemic vascular resistance / systemic vascular resistance index
- Stroke volume variation

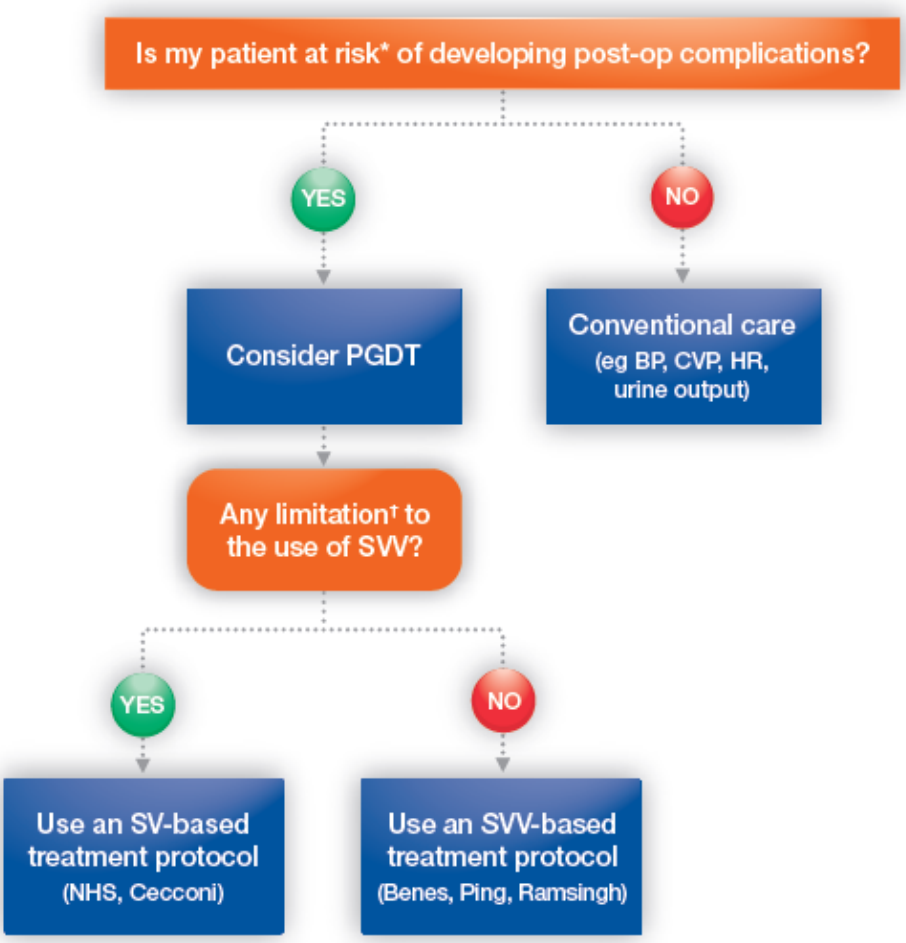
3.2.3 Contraindications or limitations on use

FloTrac has not been validated in artificial hearts and ventricular assist devices (VAD). The FloTrac sensor is currently not validated or labeled for use in children. Inaccurate CO measurements can be caused by intraaortic balloon pumps (IABP). Severe, persistent arrhythmias may affect accuracy. Severe, persistent peripheral vasoconstriction or arterial spasm, e.g. in patients with shock, may dampen the arterial waveform resulting in erroneously low CO values. Central arterial access (e.g. femoral access) is recommended in such conditions.

3.2.4 Fluid management protocol

Edwards Lifesciences describe using fluid challenges in cases where fluid responsiveness cannot be determined by assessing SVV or performing a passive leg raise. Edwards Lifesciences do not recommend a specific protocol but provides examples of protocols that were used in published randomised trials. The manufacturer provides a decision aid to assist clinicians in choosing an intraoperative fluid management protocol (Figure 2).

Figure 2: 'Considering a protocol' (Edwards Lifesciences), reproduced from Edwards Critical Care Education: Perioperative Goal-Directed Therapy, Protocol Summary. (Edwards Critical Care Education 2013)



*At risk because of comorbidities or the surgical procedure itself.

†Limitations to the use of SVV: Spontaneous breathing, tidal volume <7 ml/kg, open chest, atrial fibrillation, right ventricular failure, and laproscopic surgery.

3.3 LiDCO*plus*

3.3.1 Components

The LiDCO*plus* monitor is intended for use in patients with arterial and venous (peripheral or central) line access. It is a large screen monitor suitable for viewing at a distance. LiDCO*plus* is compatible with commonly used arterial and venous access products. The system also uses a single point lithium dilution calibration system: this is a small device containing a lithium sensitive electrode in a flow through cell, which connects to the arterial line via a three-way tap.

3.3.2 Technical basis of operation

LiDCO*plus* measures arterial pressure. The integral PulseCO software calculates cardiac output based on a beat-to-beat analysis of the whole arterial pressure waveform. Other measured parameters include:

- Body Surface Area
- Mean, systolic and diastolic pressure
- Heart rate
- Heart rate variation
- Systolic Pressure Variation
- Pulse Pressure Variation
- Cardiac Output / Index
- Stroke Volume / Index
- Stroke Volume Variation
- Systemic Vascular Resistance / Index
- Oxygen delivery / Index

A check on calibration is recommended every 24 hours of use and ensures highly accurate measurement. Calibration is as follows. The uncalibrated LiDCO*plus* monitor displays the pre calibration cardiac output (COa). Isotonic lithium chloride (150mM) is injected as a bolus (0.3 mmol) via a peripheral or central vein. The ion-selective electrode on the arterial line generates a concentration-time curve. A highly accurate measure of cardiac output (COk) is given by the formula:

$$Cok = \frac{Lithium\ dose\ (mmol)\ x\ 60}{Area\ x\ (1 - PCV)(mmol/s)}$$

Where 'Area' is the integral of the primary lithium dilution curve and 'PCV' is packed red cell volume. The equation takes account of PCV because lithium travels only in the plasma component of the blood.

The correlation factor (CF), is calculated as follows:

$$CF = \frac{COk}{COa}$$

3.3.3 Contraindications or limitations on use

Contraindications to LiDCO*plus* calibration procedure are patients undergoing treatment with lithium salts, patients who are less than 40kg (88lb) in weight and patients in the first trimester of pregnancy. The software which derives SV and CO requires that the arterial pressure data be derived from an artery that is not compromised by severe peripheral arterial vasoconstriction/vasospasm, by the concurrent use of an aortic balloon pump or by aortic valve regurgitation. Severe hyponatraemia and the use of quarternary ammonium ion containing neuro-muscular blockers can hamper calibration.

3.3.4 Fluid management protocol

There are a number of fluid management protocols available in the literature that can be used with the LiDCO*plus* monitor, targeting for example, oxygen delivery, cardiac output, stroke volume or stroke volume index and preload responsiveness parameters.

3.4 LiDCO*rapid*

3.4.1 Components

The LiDCO*rapid* has a smaller screen than the LiDCO*plus* and requires either an existing radial artery line, or it may be used with non invasive blood pressure measurement.

3.4.2 Technical basis of operation

LiDCO*rapid* uses the same PulseCO software as LiDCO*plus* (see section), and therefore derives beat-to-beat cardiac output and related parameters from arterial pressure measured over the over the entire cardiac cycle.

LiDCO*rapid* provides continuous monitoring of the following parameters:

- Nominal Cardiac Output/ Index
- Nominal Stroke volume / Index
- Mean, systolic and diastolic arterial pressure
- Heart Rate
- Heart rate variation
- Pulse Pressure Variation
- Stroke Volume Variation
- Systemic Vascular Resistance / Index

LiDCO*rapid* does not use calibration by lithium dilution but estimates a correlation factor from a nomogram using the patient's age, height and weight, in which case, the cardiac output and stroke volume parameters are no longer designated as nominal.

3.4.3 Contraindications or limitations on use

LiDCO*rapid* is not approved for use in patients < 40kg (88lbs) in weight. The software which derives SV and CO requires that the arterial pressure data be derived from an artery that is not compromised by severe peripheral arterial vasoconstriction/vasospasm, by the concurrent use of an aortic balloon pump or by aortic valve regurgitation.

3.4.4 Fluid management protocol

There are a number of fluid management protocols available in the literature that can be used with LiDCO*rapid,* targeting for example, cardiac output, stroke volume or stroke volume index and preload responsiveness parameters.

3.5 PiCCO

3.5.1 Components

PiCCO is a complete haemodynamic monitoring system for patients in critical care. The technology comprises a monitor and requires patients to have both a disposable arterial catheter and a central venous catheter. Arterial catheters can be placed in the femoral, brachial and axilla arteries.

3.5.2 Technical basis of operation

PiCCO provides continuous arterial pressure measurement and derives pulse contour cardiac output (PCCO) based on heart rate and stroke volume. Stroke volume is derived from the PiCCO pulse contour algorithm. Stroke volume variation is derived from calculation of stroke volume over several respiratory cycles.

PiCCO utilises calibration of the pressure derived cardiac output by periodic transpulmonary thermal dilution. A bolus of cold saline is injected to the central vein which passes through the cardiopulmonary circulation and the temperature is measured at the arterial line. The transpulmonary thermodilution curve enables a very accurate measurement of cardiac output, averaged over several respiratory cycles to minimise deviation.

Parameters displayed:

- Pulse Contour Cardiac Output / Index
- Cardiac Output / Index
- Stroke Volume SV / Index
- Heart Rate HR
- Mean Arterial Pressure MAP
- Arterial Pressure AP
- Systemic Vascular Resistance / Index SVR
- Global End-Diastolic Volume / Index GEDV
- Intrathoracic Blood Volume / Index ITBV
- Stroke Volume Variation SVV
- Pulse Pressure Variation PPV
- Extravascular Lung Water / Index EVLW
- Pulmonary Vascular Permeability Index PVPI
- Contractility Global Ejection Fraction GEF
- Cardiac Function Index CFI
- Index of Left Ventricular Contractility dP/mx
- Cardiac Power Output /Index CPI
- R15 – ICG Retention Rate after 15 minutes[2] R15
- Plasma Disappearance Rate of ICG[2] PDR
- Central venous oxygen saturation[1] $SCV0_2$ *
- Oxygen Supply [1] DO_2
- Oxygen Consumption [1] VO_2
- Arterial Oxygen Saturation[2] $SP0_2$

[1] measured with CeVOX module 2 measured with LiMON module

* Requires a CeVOX fibreoptic probe which is placed using the distal lumen of the CVC.

3.5.3 Contraindications or limitations on use

There are no absolute contraindications however, the usual precautions should be considered when accessing large vessels. The PiCCO catheter carries the risks that are associated with any arterial catheter e.g. puncture injury, infection (rare), impaired blood flow, haematoma. Care should be taken in cases of coagulation problems, or vascular grafts. Alternative arterial sites can be used.

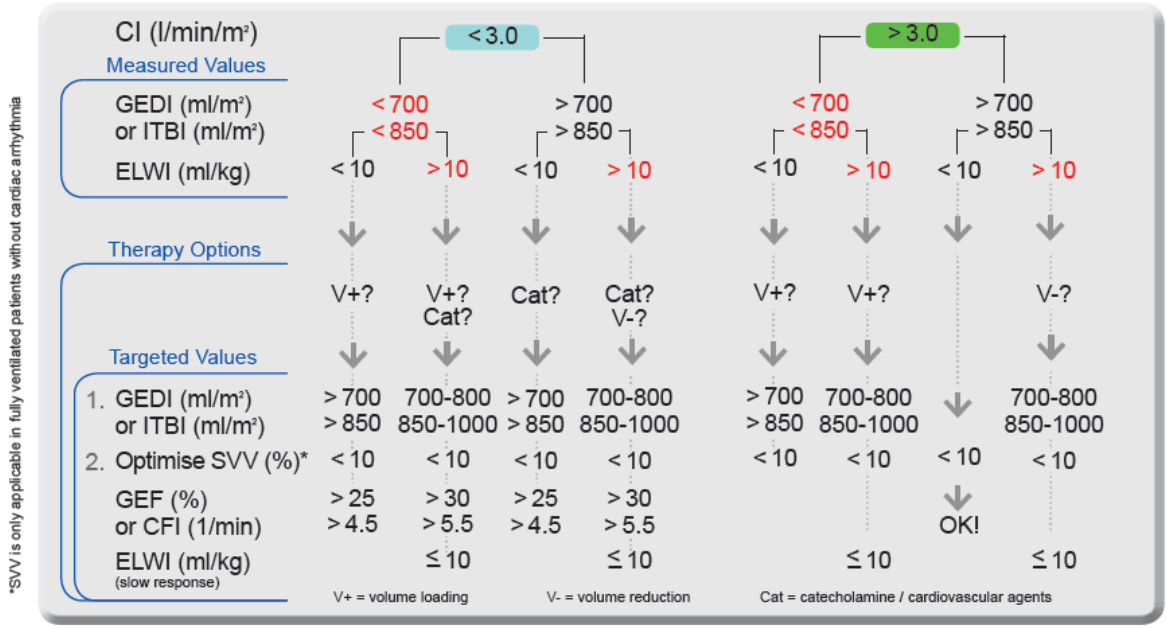
The maximum recommended placement period for a PiCCO catheter is 10 days although under the CE mark this is stated as 28 days. As normal saline is used for thermodilution measurements, there are no restrictions on the number of measurements possible, including in pregnant women and in children.

3.5.4 Fluid management protocol

PiCCO provides a fluid protocol (Figure 3) based on the parameters:

- global end diastolic index (GEDI)
- intrathoracic blood volume index (ITBI)
- extravascular lung water index (ELWI)
- cardiac function index (CFI)

Figure 3: PiCCO fluid management protocol (reproduced with permission of PiCCO)



3.6 Pleth Variability Index (PVI)® on Masimo Radical-7®

3.6.1 Components

Pleth Variability Index (PVI), displayed on the Masimo Radical-7 pulse oximeter, is a non-invasive, continuous hemodynamic index to help manage fluid responsiveness in ventilated patients. PVI, along with the other non-invasive monitoring technologies available with the Masimo rainbow SET® platform enables the assessment of multiple blood constituents and physiologic parameters that previously required invasive procedures. Therefore, as a pulse oximeter, the Radical-7 may be used in numerous hospital settings.

The Radical-7 consists of a small, portable battery or mains operated monitor and a non-invasive finger sensor. The monitor permits hand held operation and has gravity-activated screen rotation. Reusable and disposable probes are available with the latter recommended for theatre use because they fix to the finger with adhesive film and reliably stay in place under theatre drapes. The Radical-7 connects to other patient monitoring systems via cable or wirelessly via WiFi (802.11 a/b/g) for ambulatory patients.

3.6.2 Technical basis of operation

The Masimo Radical-7 is an upgradeable pulse oximeter that can measure and display the following parameters:

- Oxygen Saturation (SpO_2)
- Pulse Rate (PR)
- Perfusion Index (PI)
- Pleth Variability Index (PVI)
- Haemoglobin (SpHb)
- Oxygen Content (SpOC)
- Carboxyhaemoglobin (SpCO)
- Methaemoglobin (SpMet)
- Respiration Rate Over the Pleth (RRp)
- Acoustic respiration rate (RRa)

PVI is a numerical index that corresponds to the variation in the photoplethysmographic waveform amplitude over the respiratory cycle. It has been demonstrated that under certain conditions (ventilated adult patient, Vt >8ml/kg, no movement, no arrhythmias, no RV or LV dysfunction) PVI can be used to determine whether a patient will be fluid responsive.

With Masimo's signal extraction technology (SET®), the Radical-7 pulse oximeter uses a sensor placed on an extremity (such as a finger) that emits visible red and infrared light. The light travel through the tissue and is received by a sensor at the other side of the probe. The light detected by the sensor is used to determine many parameters including blood- oxygen saturation as well as perfusion Index (PI). The latter is a measure of the blood flow detected through the extremity and is calculated as:

PI (%) = AC/DC x 100

Where:

- DC is a constant amount of light that is absorbed by skin, bone, and other tissues including nonpulsatile blood.
- AC is a variable amount of light that is absorbed by pulsating blood flow over the cardiac cycle.

The Radical-7 uses variation in PI over the respiratory cycle to calculate the Pleth Variability Index (PVI). PVI (%) = $(PI_{max} – Pi_{min})/PI_{max}$ x 100

PVI is of value because cyclic changes in the plethysmogram reflect cyclic changes in blood pressure which in turn, reflect changes in intravascular volume (ref tech bulletin 3). Therefore, the lower the PVI value, the less variability there is in the PI over the respiratory cycle. Conversely high PVI indicates that there is high variability in PI over the respiratory cycle and in the conditions listed previously may indicate the presence of hypovolaemia.

PVI is available on other Masimo devices (Rad-87 / Rad-57) and on numerous multi-parameter monitors located in the operating theatre which use Masimo SET such as the Dräger Infinity monitor.

3.6.3 Contraindications or limitations on use

The Radical-7 can be used in all patient settings, however, as a stand-alone device is not indicated for use as an apnea monitor. PVI, when used under specific conditions, such as ventilated adult patients, with a tidal volume >8ml/kg, no movement, no arrhythmias, and no or minimal cardiac dysfunction, has been identified as a haemodynamic monitor by independent researchers (Forget et al. 2010, Forget et al. 2013). However, Masimo does not market the Radical-7 device as for use in GDT.

3.6.4 Fluid management protocol

There is no specific protocol provided by Masimo, although protocols have been used with PVI in randomised trials. Essentially, in such protocols, and in mechanically ventilated patients, high PVI levels (about 12-15%) have been shown to be predictive of fluid responsiveness, that is, an increase in cardiac output is observed when the patient is given a fluid bolus.

3.7 ProAQT with PulsioFlex

3.7.1 Components

The ProAQT sensor provides cardiac output monitoring via a standard arterial catheter and is intended for perioperative monitoring of high risk patients or patients undergoing high risk surgery. The ProAQT sensor works with the PulsioFlex modular monitoring system. PulsioFlex can also become a full PiCCO monitor with the addition of the PiCCO module which attaches to the rear of the monitor. PulsioFlex with ProAQT can be used for ICU, theatres, A&E, trauma, liver units and cardiac. With the PiCCO module attached all the parameters for PiCCO are available.

3.7.2 Technical basis of operation

ProAQT derives CO from direct arterial pulse pressure measurement. Manual and automatic calibration are possible. The following parameters are displayed:

- CO, CI, SVI
- SVV, PPV
- SVRI, MAP
- dPmax, CPI
- R15 – ICG Retention Rate after 15 minutes2 R15
- Plasma Disappearance Rate of ICG2 PDR
- Central venous oxygen saturation1 $SCV0_2$ *
- Oxygen Supply 1 DO_2
- Oxygen Consumption [1] VO_2

- Arterial Oxygen Saturation[2] SPO_2

[1] measured with CeVOX module

[2] measured with LiMON module

* Requires a CeVOX fibreoptic probe which is placed using the distal lumen of the CVC.

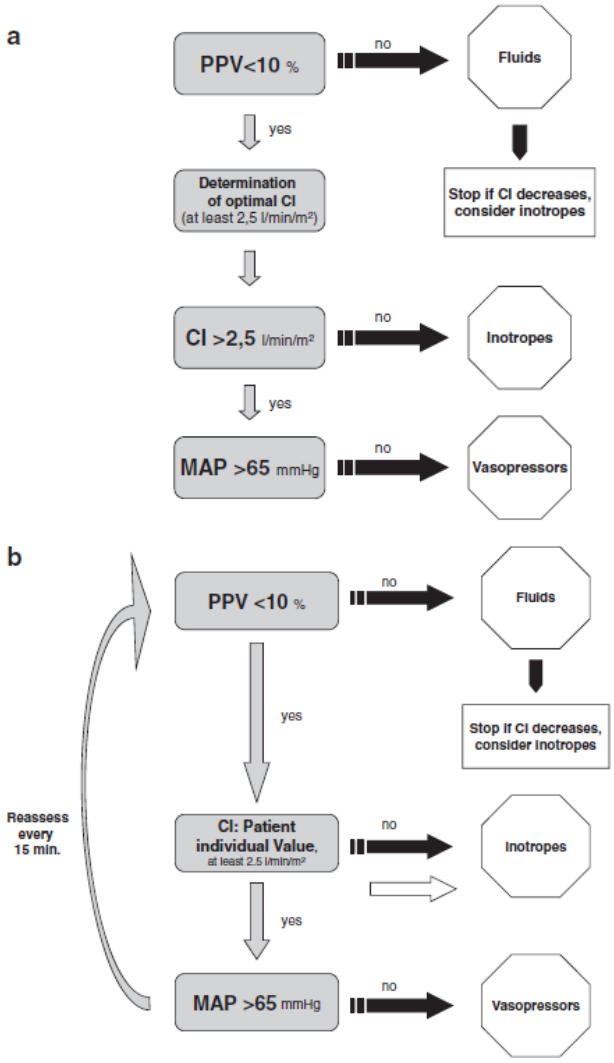
3.7.3 Contraindications or limitations on use

The widely recognised risks associated with arterial puncture apply e.g. puncture injury, infection (rare), impaired blood flow, haematoma.

3.7.4 Fluid management protocol

The fluid protocol incorporates PPV, CI and MAP, and prompts the use of fluid loading and inotropes/vasopressors (Figure 4).

Figure 4: ProAQT fluid management protocol



a = initial assessment, b = further intraoperative optimisation.

4 Results of the RCT review

4.1 Study selection process

The literature searches were performed in August 2013 and the results are shown for each database in Table 3. Bibliographic information for all studies was imported to a Reference Manager v12 database.

Table 3: Literature search results by electronic database

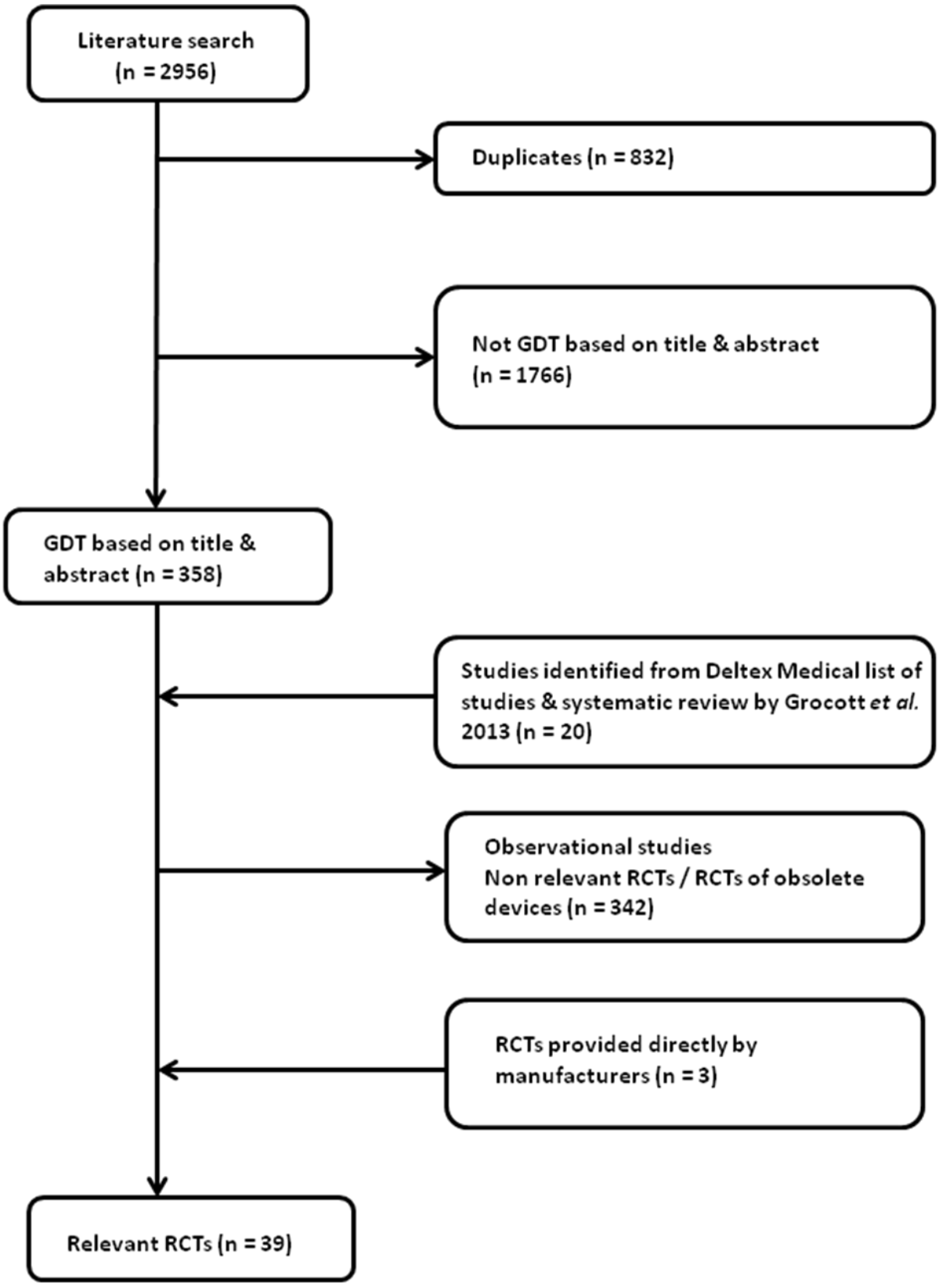
Technology group	Medline (since 1946)	Embase (since (1974)	HMIC (since 1979)	Total
Doppler	109	362	0	471
Impedance	286	1033	0	1319
Pulse pressure waveform analysis	397	769	0	1166
Total				2956

Figure 5 shows the study selection process. After excluding 832 duplicates, a further 1766 studies were not evaluating GDT, based on their titles and abstracts. This left 358 studies that, based on their titles and abstracts, showed potential for being studies of GDT, for example by:

- using a relevant technology
- evaluating the usefulness of haemodynamic parameters to predict fluid responsiveness ('validation' studies)
- evaluating the role of specific fluid regimes.

We excluded all observational studies, and we identified 20 additional RCTs from Grocott *et al.* (2013) and the Deltex Medical list. We received 3 RCTS directly from manufacturers, resulting in 39 relevant, randomised trials (Figure 5).

Figure 5: study selection flowchart



4.2 The nature of the evidence

The included 39 studies have significant differences in their characteristics that reflect a description of the RCT evidence base in a recent systematic review of generic GDT (Grocott *et al.* 2013) as follows:

- Case mix of patients recruited (including surgical risk)
- The specific parameters targeted for GDT (this varies across different technologies and across different studies of the same technology)
- The fluids and drugs administered to achieve the goals (sometimes inotropic and vasopressor drugs are within protocols, other times they are left to the clinician's discretion)
- The management of the control arm.

In general the attribution of clinical benefits directly to GDT technologies is difficult because the research is heavily confounded. The 39 trials included in this review span a long time period from the year 1995 to September 2013, and the publication of GDT research appears to be proliferating. In the UK and other countries standard perioperative care has improved. In a considerable number of studies the control arms are using more sophisticated parameters to set the baseline against which to evaluate the 'novel' GDT technology. It can be argued that in the era of ERP it is more difficult for a GDT technology to show a benefit over (enhanced) standard care. However ERP may not be implemented uniformly across the NHS or across different surgical specialities. Some of the fluid strategies examined in the trials may have low applicability to the NHS because of changes over time, or different approaches used in different countries.

A common factor that varies across studies is the amount of non protocol fluid administered, in either study arm. We have reported the volumes of different perioperative fluids administered as an interim outcome measure.

Comparative studies of GDT sit alongside a wider debate among researchers about whether crystalloid or colloid fluids are better for surgical patients. The majority of GDT fluid protocols use colloid fluid challenges, although commonly, a 'maintenance' infusion of crystalloid was also given, sometimes within the fluid protocol and sometimes independently of the fluid protocol.

Some types of hydroxyethyl starch (HES) colloid fluid have been recently withdrawn from use in the UK by the Medicines and Healthcare Products Regulatory Agency (MHRA). HES is commonly used in the included trials.

A minority of the included trials examine GDT in the immediate postoperative period. These trials were included because immediate postoperative GDT could plausibly affect perioperative outcomes. The operating theatre environment may present greater ergonomic challenges and time pressure on clinical staff than the postoperative critical care environment. It therefore does not automatically follow that because a technology is shown to work in one area, it will be practical to use in another.

Detailed data and comments based on critical appraisal of each study are available in evidence tables, accessible via hyperlinks in the sections that follow.

5 RCT evidence for the technologies

5.1 CardioQ-ODM

5.1.1 The studies

Sixteen randomised trials were identified for CardioQ-ODM (Brandstrup *et al.* 2012; Challand *et al.* 2012; El Sharkawy *et al.* 2013; Feldheiser *et al.* 2013; Gan *et al.* 2002; McKendry *et al.* 2004; McKenny.M. *et al.* 2013; Mythen & Webb 1995; Noblett *et al.* 2006; Pillai *et al.* 2011; Senagore *et al.* 2009; Sinclair *et al.* 1997; Srinivasa *et al.* 2013; Venn *et al.* 2002; Wakeling *et al.* 2005; Zakhaleva *et al.* 2013). These are summarised in Table 4.

Fourteen trials use CardioQ-ODM for GDT intraoperatively and two for postoperative GDT (El Sharkawy *et al.* 2013; McKendry *et al.* 2004). The study by El Sharkawy et al. (2013) initiated GDT following liver resection and continued for 24 hours postoperatively.

One recently published trial (Feldheiser *et al.* 2013) uses CardioQ-ODM to compare colloid based GDT with crystalloid based GDT and therefore does not evaluate CardioQ-ODM against standard care. This study found the two fluid protocols to be equivalent for complications and length of hospital stay.

Intraoperative GDT – length of hospital stay

For intraoperative GDT, thirteen trials compare CardioQ-ODM guided GDT with standard care. Of these, six (Gan *et al.* 2002; Mythen & Webb 1995; Noblett *et al.* 2006; Sinclair *et al.* 1997; Venn *et al.* 2002; Wakeling *et al.* 2005) show clear benefits for CardioQ-ODM over standard care for reduced hospital stay (in one study of patients with hip fracture (Venn *et al.* 2002) this was expressed as time to fitness for discharge). Differences in length of stay between arms range from 1.5-8 days.

Six trials found no difference in length of stay between CardioQ-ODM guided GDT and standard care (Brandstrup *et al.* 2012; Challand *et al.* 2012; McKenny.M. *et al.* 2013; Pillai *et al.* 2011; Srinivasa *et al.* 2013; Zakhaleva *et al.* 2013).

One trial found hospital stay to be shorter in the standard care arm than in two GDT arms, both using CardioQ-ODM (Senagore *et al.* 2009). However the differences involved were small: 7 hours and 11 hours.

Intraoperative GDT – complications

Of the thirteen trials comparing CardioQ-ODM guided GDT with standard care, six trials (Gan *et al.* 2002; Mythen & Webb 1995; Noblett *et al.* 2006; Pillai *et al.* 2011; Wakeling *et al.* 2005; Zakhaleva *et al.* 2013) favour CardioQ-ODM over standard care for reduced complications and seven found no difference or did not report complications (Brandstrup *et al.* 2012; Challand *et al.* 2012; McKenny.M. *et al.* 2013; Senagore *et al.* 2009; Sinclair *et al.* 1997; Srinivasa *et al.* 2013; Venn *et al.* 2002).

Postoperative GDT

In the immediate postoperative setting, two trials show a benefit arising from CardioQ-ODM in reduced hospital stay of 1.3-2 days compared to standard care (El Sharkawy *et al.* 2013; McKendry *et al.* 2004). Data in one study were suggestive of reduced complications from CardioQ-ODM, but with no statistical analysis (McKendry *et al.* 2004) and in the other study there was a lower rate of postoperative nausea and vomiting in the GDT arm (El Sharkawy *et al.* 2013).

5.1.2 Interpretation

The trials span an 18-year publication period and the control arms evolved somewhat in that time. One trial states that both arms were treated within an enhanced recovery programme (Challand *et al.* 2012) and two trials used fluid restriction or zero balance protocols in the control arms (Brandstrup *et al.* 2012; Srinivasa *et al.* 2013). The GDT protocols used for CardioQ-ODM are highly similar: all use SV, many use FTc in addition and most are colloid-based. A minority incorporate MAP, CVP and explicitly stipulate use of inotropes/vasoactive drugs.

Table 4: randomised trials of CardioQ-ODM guided GDT used intraoperatively or immediately postoperatively

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of hospital stay[1]
Brandstrup (2012)	Intraoperative GDT Bowel	GDT versus zero fluid balance (GDT protocol: SV, colloid)	No difference	No difference
Challand (2012)	Intraoperative GDT Bowel	GDT versus standard care (GDT protocol: SV, colloid)	No difference	No difference
El Sharkawy 2013	Postoperative GDT Liver surgery	GDT versus standard care (GDT protocol: Ftc, SV, colloid)	Favours GDT for postoperative nausea & vomiting	Favours GDT, difference 1.3 days
Feldheiser (2013)	Intraoperative GDT Ovarian	GDT (colloid) versus GDT (crystalloid) (GDT protocol: SV, FTc, MAP, vasopressor, inotrope)	No difference	No difference
Gan (2002)	Intraoperative GDT General	GDT versus standard care (GDT protocol: SV, Ftc, colloid)	Favours GDT for nausea/vomiting. No difference in other complications	Favours GDT (difference 2 days)
McKendry (2004)	Postoperative GDT Cardiac	GDT versus standard care (GDT protocol: SVI, MAP, colloid, epinephrine, nitrate)	No analysis	No difference
McKenny (2013)	Intraoperative GDT Gynaecology	GDT versus standard care (GDT protocol: SV, colloid)	No difference	No difference

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of hospital stay[1]
Mythen (1995)	Intraoperative GDT Cardiac	GDT versus standard care (GDT protocol: SV, CVP, colloid)	Favours GDT	Favours GDT (difference 3.7 days)
Noblett (2006)	Intraoperative GDT Bowel	GDT versus standard care (GDT protocol: SV, FTc, colloid)	Favours GDT for major complications, ileus, nausea/vomiting and need for critical care.	Favours GDT (difference 2 days)
Pillai (2011)	Intraoperative GDT Bladder	GDT versus standard care (GDT protocol: SV, FTc, colloid)	Favours GDT	No difference
Senagore (2009)	Intraoperative GDT Bowel	GDT (colloid) versus GDT (crystalloid) versus standard care (GDT protocol: SV)	No difference	Very small observed differences. Favoured standard care
Sinclair (1997)	Intraoperative GDT Hip fracture	GDT versus standard care (GDT protocol: SV, FTc, colloid)	No data	Hospital stay favours GDT (difference 8 days). Time to fitness for discharge favours GDT (difference 5 days)
Srinivasa (2013)	Intraoperative GDT Bowel	GDT versus fluid restrictive protocol (GDT protocol: SV, FTc, colloid)	No difference	No difference
Venn (2002)	Intraoperative GDT Hip fracture	GDT (SV) versus GDT (CVP) versus standard care (GDT protocol: SV, FTc, colloid)	No difference	No difference in hospital stay. Time to fitness for discharge favours GDT
Wakeling (2005)	Intraoperative GDT Bowel	GDT versus standard care (GDT protocol: SV, CVP, colloid)	Favours GDT	Favours GDT
Zakhaleva (2013)	Intraoperative GDT Bowel Enhanced recovery programme	GDT versus standard care (GDT protocol: SV, FTc, colloid)	Favours GDT	No difference

[1] This is reported as length of hospital stay in all studies except in McKenny et al. (2013): time to readiness for discharge; Noblett et al. (2006): postoperative hospital stay; Wakeling et al. (2005): postoperative hospital stay.

5.2 FloTrac

5.2.1 The studies

Ten randomised trials of FloTrac-guided GDT were included (Benes *et al.* 2010; Cecconi *et al.* 2011; Kapoor *et al.* 2008; Mayer *et al.* 2010; Ramsingh *et al.* 2013; Scheeren *et al.* 2013; Van Der Linden *et al.* 2010; Wang *et al.* 2012; Zhang *et al.* 2013; Zheng *et al.* 2013). These are summarised in Table 5.

Intraoperative GDT

Two trials found a difference in length of hospital stay in favour of FloTrac guided GDT over standard care with a difference of between 2.5-4 days (Mayer *et al.* 2010; Ramsingh *et al.* 2013). One trial (Benes *et al.* 2010) found that FloTrac guided GDT shortened hospital stay by 1 day, but only in a per protocol analysis (not in the intention-to-treat analysis). Four trials found no difference in hospital or critical care stay between FloTrac guided GDT and standard care (Cecconi *et al.* 2011; Scheeren *et al.* 2013; Van Der Linden *et al.* 2010; Zhang *et al.* 2013).

Two trials demonstrated a clear benefit from FLoTrac guided GDT compared to standard care in reducing postoperative complications (Benes *et al.* 2010; Mayer *et al.* 2010). One trial found that wound infections were reduced in the FloTrac arm compared to standard care, but not general complications (Scheeren *et al.* 2013). One study demonstrated a lower rate of postoperative nausea/vomiting in the FloTrac group compared to standard care, but with no difference in other complications (Zhang *et al.* 2013). Another study found a lower rate of minor complications in the FloTrac arm compared to the control arm, but with no difference in major complications (Cecconi *et al.* 2011). The remaining studies (Ramsingh *et al.* 2013; Van Der Linden *et al.* 2010; Wang *et al.* 2012) found no difference in complications between groups, or provided no analysis, but one study found that bowel recovery after surgery was quicker in the GDT arm (Ramsingh *et al.* 2013).

Intra/postoperative GDT

The study by Zheng *et al.* 2013 compared FloTrac guided GDT with standard care in elderly patients undergoing gastrointestinal surgery, where GDT was continued for 24 hours postoperatively. There was no significant difference in the rate of adverse cardiac events between groups. Bowel function outcomes postoperatively favoured the FloTrac group as did the rate of nausea and vomiting. ICU stay and hospital stay were shorter in the FloTrac group (Zheng *et al.* 2013).

Postoperative GDT

One trial found no difference in length of hospital stay between FloTrac guided GDT and standard care (Kapoor *et al.* 2008). This study did not analyse complications.

5.2.2 Interpretation

All of the trials are recent publications, within the last three years. The patient groups studied are those who require invasive monitoring with peripheral arterial catheters and often, central venous

catheters. There is considerable variation in the GDT protocols used in the trials. Most protocols are complex, the most commonly used parameters being SVV and SV. One study used a protocol in the control arm as well as the GDT arm (Cecconi *et al.* 2011) and another study used GDT in both arms, targeting different ranges of SVV to compare a liberal versus restrictive fluid protocol (Wang *et al.* 2012). This study found a shorter length of stay in the restrictive protocol group, but did not describe the method for giving fluid challenges in response to SVV and is somewhat unclear.

Table 5: randomised trials of FloTrac guided GDT used intraoperatively or immediately postoperatively

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of stay
Benes 2010	Intraoperative GDT General	GDT versus standard care (GDT protocol: SVV, CI, CVP, colloid, inotrope)	Favours GDT	No difference by intention to treat. By per protocol analysis favours GDT, difference 1 day
Cecconi 2011	Intraoperative GDT Hip replacement	GDT versus protocol with MAP, vasoactive drug, colloid) (GDT protocol: SV, HR, DO_2I, colloid, inotrope)	Favours GDT for minor complications, no difference for major complications	No difference
Kapoor 2008	Postoperative GDT Cardiac	GDT versus standard care (GDT protocol: SVV, CI, CVP, $ScvO_2$, haematocrit, colloid, inotrope, vasoactive drug, blood)	No analysis	No difference
Mayer 2010[1]	Intraoperative GDT General	GDT versus standard care (GDT protocol: CI, MAP, SVI colloid, inotrope, vasoactive drug)	Favours GDT	Favours GDT (difference 4 days)
Ramsingh 2013	Intraoperative GDT Major abdominal	GDT versus standard care (GDT protocol: SVV, CO, colloid, crystalloid)	No analysis of complications; bowel recovery favours GDT	Favours GDT (difference 2.5 days)
Scheeren 2013	Intraoperative GDT High risk surgery	GDT versus standard care (GDT protocol: SVV, SV, colloid)	Wound infection favours GDT. No difference for general complications	No difference in critical care stay
van der Linden 2010	Intraoperative GDT Vascular	GDT versus standard care (GDT protocol: SVV, CI, CVP, colloid, inotrope)	No difference	No difference
Wang 2012	Intraoperative GDT General	GDT liberal (SVV 5-7%) versus GDT restrictive (SVV 11-13%) Protocols do not specify fluids	No analysis	Favours restrictive protocol

[1] One co-author in the study by Mayer et al. (2010) has received media attention for having publications retracted by journals due to lack of trial approvals; however the included study has had its approval status confirmed by a group of Editors-in-Chief of medical journals.
http://www.aaeditor.org/EIC.Joint.Statement.on.Retractions.pdf

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of stay
Zhang 2013	Intraoperative GDT Lung surgery	GDT versus standard care (GDT protocol: SVV, CI, colloid, crystalloid, inotrope)	Favours GDT for nausea/vomiting, no difference for other complications	No difference
Zheng 2013	Intra/postoperative GDT Gastrointestinal surgery in elderly patients	GDT versus standard care (GDT protocol: MAP, SVI, colloid, crystalloid, vasoactive drug, dopamine)	Favours GDT for nausea/vomiting and bowel function recovery. No difference in cardiac events	ICU stay favours GDT, difference 15 h. Hospital stay favours GDT, difference 4 d

5.3 LiDCO*plus*

5.3.1 The studies

Six randomised trials were included (Bartha *et al.* 2013; Bisgaard *et al.* 2013; Harten *et al.* 2008; Jhanji *et al.* 2010; Lobo *et al.* 2011; Pearse *et al.* 2005). These are summarised in Table 6. Five trials are of LiDCO*plus* guided GDT versus standard care. One trial compared two LiDCO*plus* guided protocols: a conventional versus restrictive fluid protocol (Lobo *et al.* 2011). The study by Harten *et al.* (2008) studied patients undergoing emergency surgery.

Intraoperative GDT

Three trials (Bartha *et al.* 2013; Bisgaard *et al.* 2013; Harten *et al.* 2008) did not demonstrate a clear advantage of LiDCO*plus* guided GDT over control in terms of complications and length of hospital stay, although one of these trials found LiDCO*plus* to be superior to control for complications, when analyses were adjusted for demographic/comorbidity factors, or when analysis was restricted to fluid related complications (Bisgaard *et al.* 2013). One trial used LiDCO*plus* guided GDT in both arms and found that a restrictive fluid protocol was superior to a conventional protocol for the number of patients with complications, but not for total complications or length of stay outcomes (Lobo *et al.* 2011).

Postoperative GDT

One trial strongly favoured LiDCO*plus* over standard care in terms of a difference in length of stay of 3 days, and a reduced rate of complications following major surgery (Pearse *et al.* 2005). A second three arm trial found no differences in complication rates or length of hospital stay between LiDCO*plus* guided GDT, LiDCO*plus* guided GDT with inotrope and standard care.(Jhanji *et al.* 2010).

5.3.2 Interpretation

There is a significant degree of heterogeneity across the five trials. In one study LiDCO*plus* guided GDT was used intraoperatively and continued postoperatively (Bisgaard *et al.* 2013). Control arm

fluid management varied across the studies in terms of whether a fluid protocol was used and its complexity. One study was of elderly patients with fractured neck of femur and this study stated that both arms were treated within an enhanced recovery programme (Bartha *et al.* 2013). The study by Lobo et al. (2011) varied only the rate of infusion of crystalloid between arms. In two studies the authors acknowledged, based on sample size calculations, that their studies did not have adequate statistical power to detect a clinically important difference in complications between groups (Bartha *et al.* 2013; Jhanji *et al.* 2010).

Table 6: randomised trials of LiDCO*plus* guided GDT used intraoperatively or immediately postoperatively

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of stay
Bartha 2012	Intraoperative GDT Hip fracture surgery (within enhanced recovery programme)	GDT versus standard care (GDT protocol: SV, DO_2I, inotrope) (Standard care protocol included inotrope)	No difference found: study is underpowered.	No difference
Bisgaard 2013	Intra/postoperative GDT Vascular surgery	GDT versus standard care (GDT protocol: SVI, DO_2I, vasoactive drug, inotrope)	Favoured GDT only when adjusted for adjusted for age, sex, ASA status and duration of ischaemia	No difference
Harten 2008	Intraoperative GDT Emergency abdominal surgery	GDT versus standard care (GDT protocol: PPV, colloid)	No difference	No difference
Jhanji 2010	Postoperative GDT General	GDT versus GDT + inotrope versus standard care (with CVP protocol) (GDT protocols: SV, colloid, ± inotrope)	No difference found: study is underpowered	No difference
Lobo 2011	Intra/postoperative GDT High risk surgery	GDT (conventional protocol) versus GDT (restrictive protocol) (Common GDT protocol in both groups, except for 12 versus 4 ml/kg/min crystalloid. The protocol used SV, DO_2, colloid, inotrope)	Favours restrictive protocol for number of patients with complications; not for total number of major complications	No difference in critical care stay

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of stay
Pearse 2005	Postoperative GDT Major surgery	GDT versus standard care (GDT protocol: SV, DO_2I, colloid, inotrope) (Standard care protocol: CVP, colloid, inotrope)	Favours GDT	Favours GDT (difference 3 days)

5.4 LiDCO*rapid*

5.4.1 The studies

Two randomised trials were included (Jones *et al.* 2013; Yates *et al.* 2013). These are summarised in Table 7.

Intraoperative GDT

A trial comparing two fluid protocols (crystalloid versus colloid) both guided by LiDCO*rapid* found no difference in complications or length of hospital stay between groups (Yates *et al.* 2013).

Postoperative GDT

One trial of an enhanced recovery programme in liver resection (which included LiDCO*rapid* guided GDT) found that the enhanced recovery programme reduced hospital stay by three days compared to standard care (Jones *et al.* 2013). There was no difference in complications between arms but bowel recovery outcomes favoured the enhanced recovery programme.

5.4.2 Interpretation

In the trial by Jones et al. (2013) the enhanced recovery programme is a complex intervention, and therefore different elements of the programme are likely to confound discerning the role of LiDCO*rapid*.

Table 7: randomised trials of LiDCO*rapid* guided GDT used intraoperatively or immediately postoperatively

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of stay
Jones 2013	Postoperative GDT Liver surgery	GDT (within enhanced recovery programme - ERP) versus standard care (no ERP) (GDT protocol: SV, colloid, crystalloid)	No difference. Bowel recovery outcomes favoured GDT/ERP	Favours GDT/ERP (difference 3 days)
Yates 2013	Intraoperative GDT Colorectal	GDT (crystalloid) versus GDT (colloid) (GDT protocol: SV, SVV, crystalloid/colloid, Geloplasma)	No difference	No difference

5.5 PiCCO

5.5.1 The studies

Two randomised trials were included (Lenkin *et al.* 2012; Smetkin *et al.* 2009), both of PiCCO guided GDT in cardiac surgery. These are summarised in Table 8.

Intraoperative GDT

The study by Lenkin *et al.* 2012 compared PiCCO guided GDT with GDT guided using a pulmonary artery catheter. There was no analysis of postoperative complications or hospital stay, but duration of respiratory support favoured the PiCCO group.

Intra/postoperative GDT

The study by Smetkin *et al.* 2009 compared PiCCO guided GDT with standard care (based on a complex fluid protocol). In each group the protocols were followed to 6 hours postoperatively. The study found no difference postoperative complications, though hospital stay was shorter in the PiCCO guided GDT group.

5.5.2 Interpretation

Both studies used complex fluid protocols in both arms, using multiple parameters for GDT and stipulating use of inotropic or vasoactive drugs.

Table 8: randomised trials of PiCCO guided GDT used intraoperatively or immediately postoperatively

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of stay
Lenkin 2012	Intraoperative GDT Cardiac	GDT (PiCCO) versus GDT (PAC) (PiCCO protocol: GEDVI, EVLWI, MAP, CI, DO_2I, colloid, inotrope, vasoactive drug) (PAC protocol: PAOP, MAP, CI, Hb, colloid, vasoactive drugs, diuretic, inotrope)	No analysis	No difference (duration of respiratory support favours PiCCO-GDT, difference 5 h)
Smetkin 2009	Intra/postoperative GDT Cardiac	GDT versus standard care (GDT protocol: ITBVI, MAP, $ScvO_2$, Hb, CI, colloid, vasocative drugs, diuretic, verapamil, inotrope) (Standard care protocol: CVP, MAP, HR, colloid, vasoactive drugs, diuretic, verapamil, inotrope)	No difference	Favours PiCCO-GDT, difference 3 days

5.6 Pleth variability index -PVI with Masimo Radical 7

5.6.1 The studies

Two randomised trials were identified (Forget *et al.* 2010; Forget *et al.* 2013). These are summarised in Table 9. Both studies compared intraoperative PVI guided GDT versus standard care (which

included the insertion of a central venous catheter) and found no difference between groups for complications or length of hospital stay. However, these studies were possibly underpowered to detect many of these endpoints.

5.6.2 Interpretation

The study populations, non-invasive PVI based fluid protocols and invasive standard care protocols were similar in the two trials (Forget *et al.* 2010; Forget *et al.* 2013). The studies were powered to detect differences in fluids administered or lactate levels.

Table 9: randomised trials of PVI guided GDT used intraoperatively or immediately postoperatively

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of stay
Forget 2010	Intraoperative GDT General surgery	GDT versus standard care (GDT protocol: PVI, colloid) (Standard care protocol: MAP, CVP, colloid)	No difference	No difference
Forget 2013	Intraoperative GDT Bowel surgery	GDT versus standard care (GDT protocol: PVI, colloid) (Standard care protocol: MAP, colloid)	No difference	No difference

5.7 ProAQT

5.7.1 The studies

One randomised trial was identified (Salzwedel *et al.* 2013), which found that intraoperative GDT guided by ProAQT reduced postoperative complications compared to standard care (Table 10). There was no difference in hospital stay.

5.7.2 Interpretation

The study had a large sample of 160 patients drawn from four countries and was unblinded. The volumes of crystalloid, colloid and total fluid administered were similar between groups.

Table 10: randomised trials of ProAQT guided GDT used intraoperatively

Study	Setting & surgery	Comparison & GDT protocol	Complications	Length of stay
Salzwedel 2013	Intraoperative GDT Major abdominal surgery	GDT versus standard care (GDT protocol: PPV, CI, MAP, fluid, inotrope, vasopressor)	Favours GDT	No difference

6 Limitations

This review focuses only on evidence from randomised trials for reasons as follows:

- Randomised trials are the best available primary study design to determine the efficacy of the technologies.
- Existing NICE guidance on CardioQ-ODM (National Institute for Health and Care Excellence 2011) illustrated that a substantial volume of randomised controlled trial evidence for CardioQ-ODM was in existence at the time of guidance publication in 2011.
- In a rapid and pragmatic review, restricting to randomised trials provides a clear threshold for study inclusion based on study quality, while limiting the volume of evidence to be critically appraised within the timetable for the work.

A limitation of restricting to randomised trials is the omission of observational studies. Observational studies have the advantage of potentially studying large series of patients, and in the case of audits, of examining outcomes in routine care rather than in an experimental setting. A feature of new-to-market medical devices is that they are seldom supported by randomised trials and that a full evaluation may need to consider observational study data. This may apply to the technologies without published RCTs listed in Table 11, page 45. However we included 39 randomised trials of seven relevant technologies, so at least some of the available technologies for IOFM are sufficiently established to have generated a substantial volume of RCT evidence.

Similarly we excluded systematic reviews, including those that performed meta-analysis. Meta-analyses have the advantage that they can pool the results of numerous randomised trials that have similar design and study similar patient samples. This may reveal statistically significant effects that the primary studies were underpowered to detect. However we excluded the reviews to restrict to a pragmatic volume of evidence and also due to the focus of this review on individual technologies. Systematic reviews tend to study a broader family of technologies including those that no longer exist, or may include studies of GDT using any technology type.

7 Conclusions

- We identified seven technologies used for GDT (from five manufacturers) that have been used in randomised trials of GDT and a further six technologies that currently have not been studied in randomised trials.
- We identified no randomised studies directly comparing two or more technologies used for GDT.
- Interpretation of the effects of GDT studied in numerous randomised trials is complicated by differences in the case mix of patients, the fluid protocols used, the choice of fluids used (and the role of non protocol fluid), the role of inotropic / vasoactive drugs and the management of the control arm. The control arms of recently published studies may reflect modern enhanced recovery programmes. Such programmes aim to improve and standardise care for surgical patients by optimising in the perioperative period numerous aspects of care

including: patient information, nutrition, mobility and analgesia, in addition to GDT. These may confound discerning the effects of the GDT.

- Choice of a particular technology to use for GDT in a clinical setting is likely to depend upon:
    - The strength of evidence for the efficacy and safety of the technology
    - The extent of need in the patient group for invasive monitoring: the technologies offer different levels of invasive monitoring
    - Whether continuous, 'hands off' monitoring is required, or whether periodic measurement is sufficient for GDT
    - Whether manual calibration is required: manual calibration ensures high accuracy of measurement but may be time consuming in a busy operating theatre environment (but may be easier in the critical care setting).

8 Technologies available but without randomised trial evidence

There are technologies that are marketed in the UK for GDT, but currently without published randomised trials reporting data on the patient-relevant end points hospital stay and complications. These are summarised in Table 11 below.

Table 11: Technologies that have not been studied in published randomised trials

Technology	Components	Technical basis of operation	Contraindications or limitations on use	Fluid management protocol
CardioQ-ODM+ (Deltex Medical)	CardioQ-ODM+ has the same components as CardioQ-ODM but with an additional PPWA system, which permits continuous monitoring. PPWA monitoring requires patients to have an existing arterial line connected to a generic patient monitoring system. The CardioQ-ODM+ utilises the pressure data gathered by the generic system to derive pressure based parameters. The technology is intended for use in: • critical care • transfer of high risk surgical patients • surgical cases where displacement of the oesophagus may interrupt Doppler measurement or where cross-clamping of the aorta, which may interfere with Doppler measurement • prolonged periods of diathermy.	The CardioQ-ODM+ utilises the same Doppler technology and proprietary nomogram as CardioQ-ODM. The CardioQ-ODM+ provides all the standard Doppler parameters. The monitor can also provide pressure based parameters: • Cardiac Output • Cardiac Index • Stroke Volume • Stroke Volume Index • Systemic Vascular Resistance • Systemic Vascular Resistance Index • Mean Arterial Pressure • Heart Rate • Pulse Pressure Variation or Stroke Volume Variation (only one selected at any one time) Additionally the monitor can provide pressure combined parameters: • Cardiac Power (CP) • Cardiac Power Index (CPI) The pressure generated parameters require periodic calibration against the Doppler parameters. This takes < 10 seconds to perform and is achieved at the push of a button as long as a good Doppler signal is maintained for the duration of calibration. Calibration is recommended every 6-12 hours or when a change in vascular compliance is suspected.	As per CardioQ-ODM. As per hospital policy for arterial catheters.	As per CardioQ-ODM

Technology	Components	Technical basis of operation	Contraindications or limitations on use	Fluid management protocol
ccNexfin (Edwards Lifesciences)	ccNexfin is a noninvasive haemodynamic monitor, intended for patients who do not have an arterial catheter. The technology comprises a touchscreen lightweight monitor, a finger cuff connected to the wrist unit and a heart reference system permitting free movement of hand during measurement.	ccNexfin measures continuous blood pressure and uses the pulse contour method (Nexfin CO-Trek) to derive haemodynamic parameters from the continuous pressure wave Measured parameters: • Cardiac Output / Index CO / CI • Systolic / Diastolic Blood Pressure Sys / Dia • Mean Arterial Pressure MAP • Heart Rate HR • Stroke Volume /Index SV / SVI • Stroke Volume Variation SVV • Pulse Pressure Variation PPV • Systemic Vascular Resistance SVR	ccNexfin can be used in any patient. However, in some patients with extreme contraction of the smooth muscle in the arteries and arterioles in the lower arm and hand, e.g. in Raynaud's disease, blood pressure measurement can become impossible.	The technology does not have its own protocol but is able to support most protocols for fluid management.

Technology	Components	Technical basis of operation	Contraindications or limitations on use	Fluid management protocol
esCCO (Nihon Kohden)	The Nihon Kohden system uses pulse oximetry and ECG to provide continuous, noninvasive haemodynamic assessment. The system uses the LifeScope or Vismo patient monitors, which are modular systems. esCCO is intended for patients in surgery, critical care and general hospital settings.	esCCO (Estimated Continuous Cardiac Output) is the software algorithm that calculates cardiac output from pulse wave transit time (PWTT) as follows: PWTT is derived from the 3 time components; Pre-ejection Period (PEP) which is dependant on cardiac contractility, T1 (influenced by blood pressure & vascular tone) and T2 (influenced by viscosity & peripheral vascular resistance) all of which have an inverse relationship to SV. The sum of PEP, T1 & T2 is PWTT which is measured from the peak of the R wave to the 30% rise point of the SpO2 plethysmographic waveform. esCCO = K * (α * PWTT + β) * HR Where: • α is an experimental constant • β is a constant calculated from the pulse-pressure of NIBP (or from an invasive arterial pressure) • K is a constant calculated from a given CO value. • HR = heart rate The clinician enters patient data as follows: age, gender, height, weight and an initial NIBP measurement. This provides a reference value for calibration after which esCCO begins measurement. Parameters displayed: • esCCO, esCCI, esSV, esSVI. (note; esSVR & esSVRI are available if CVP is transduced - Life Scope monitors only) • HR • SpO2 • NIBP (or IBP) • etCO2 (optionally) (Note: with Life Scope monitors, a full range of multiparameter measurements are available) http://www.nihonkohden.de/index.php?id=411&L=1	esCCO may be used on any patient type in any situation. esCCO takes approximately 5 minutes to set-up and calibrate, requires no special training and has no operator bias, uses no consumables/disposables. esCCO may not be used in the following situations: Paced patients, Atrial fibrillation, frequent arrhythmia, during CP bypass, when peripheral circulation does not provide an SpO2 waveform.	The relationship between stroke volume/cardiac output changes and fluid/drug administration is well documented. esCCO & esSV measurements may be used in place of estimated values derived from other techniques and thus in existing fluid management protocols.

Technology	Components	Technical basis of operation	Contraindications or limitations on use	Fluid management protocol
ICON (Osypka Medical; UK supplier is Dot Medical)	ICON is a small, noninvasive, hand held or pole mounted cardiac output monitor. Four electrodes attach to the patient's skin on the chest and transmit electrical activity to the battery or mains operated monitor. The technology may be used in adults and children/neonates.	The principle of operation is described as Electrical Cardiometry™. Alternating current is applied towards the thorax via two outer electrodes. The resulting voltage is measured between two inner electrodes. The ratio of the current applied and the voltage measured equals the thoracic electrical conductivity, which changes characteristically during the cardiac cycle. Recorded parameters are: • Stroke Volume (SV) / Stroke Volume Index (SVI) • Stroke Volume Variation (SVV) • Heart Rate (HR) • Cardiac Output (CO) / Cardiac Index (CI) • Index of Contractility (ICON®) • Variation of Index of Contractility (VIC™) • Systolic Time Ratio (STR = PEP/LVET) • Thoracic Fluid Index (TFI) • Corrected Flow Time (FTC) • Left Ventricular Ejection Time (LVET) • Pre Ejection Period (PEP) • Systemic Vascular Resistance (SVR) / Systemic Vascular Resistance Index (SVRi) • Cardiac Power index (CPI) • Arterial Oxygen Content (CaO2) • Oxygen Delivery (DO2) / Oxygen Delivery Index (DO2I) Source: http://www.osypkamed.com/	None identified	Thoracic Fluid Index (TCI) indicates general hydration levels on a trend display over a period up to 72 hours. Normal values are 15 – 40: Values lower than 15 indicate general dehydration. Values above 50 indicate potential oedema. Stroke Volume Variation (SVV) indicates more specific fluid loss (for example; evaporation during bowel surgery) on a trend display over a period of up to 72 hours. SVV is used as an indicator for anaesthetists to provide fluids. The SVV may also prevent over use of fluids during surgical procedures. Normal values are less than 10% in a well hydrated patient. SVV starts to rise with dehydration and at 15-20% it is expected that fluids be delivered.

Technology	Components	Technical basis of operation	Contraindications or limitations on use	Fluid management protocol
NICOM (Cheetah Medical (UK Supplier: Proact Medical)	The NICOM system consists of a monitor and a series of four noninvasive sensors that are stuck on the skin of the thorax. NICOM provides continuous, non invasive haemodynamic monitoring in numerous clinical settings.	NICOM works on the principle of bioreactance. Each of the four sensors has two conductive pads, one to send the electrical signal and one to receive the signal. The NICOM monitor induces an alternating current (AC) in both the left and right sides of the thorax. The pulsating blood in the aorta causes a change in the amplitude of the applied voltage and a time delay (phase shift) between the applied current and measured voltage. Numerous phase shifts create the NICOM signal, which correlates with aortic volume. The derivative of the NICOM signal over time (dNICOM) is the flow signal dX/dt, where X is the amplitude of the voltage. Stroke volume is derived as: SV = dX/dt * VET where VET is ventricular ejection time, i.e. the time period between two zero voltage amplitudes over one systole. Cardiac output is derived as follows: CO = f(dX/dt, VET, HR, weight, height, age). The clinician enters the patient's weight, height and age to enable estimation of cardiac output. Parameters displayed: • Cardiac Output (CO) • Diastolic, systolic, and mean blood pressure • Heart rate. • Cardiac Index (CI), • Ventricular Ejection Time (VET), • Total Peripheral Resistance Index (TPRI), • Stroke Volume Index (SVI), • Stroke Volume Variation (SVV), • Cardiac Power (CP), • Cardiac Power Index (CPI), • Electrical impedance of the chest cavity (Zo) • Thoracic Fluid Content (TFC). Source: http://www.cheetah-medical.com/	The following situations may overestimate CO, influence monitor accuracy, or result in suboptimal signal quality: 1. Severe aortic insufficiency 2. Severe anatomic abnormalities of the thoracic aorta 3. External pacemakers - NICOM sensors should be at least 2.5 inches away from the percutanneous lead. Some external pacemakers can add electrical artifact to the NICOM signal.	Cheetah medical describes passive leg raising (PLR) as a means to test fluid responsiveness. and states that in cases where PLR is not possible, assessing change in Stroke Volume Index following the administration of 250ml fluid bolus determines fluid responsiveness.

Technology	Components	Technical basis of operation	Contraindications or limitations on use	Fluid management protocol
Uscom 1A (UK supplier Genesys)	Haemodynamic monitor plus noninvasive, reusable transducer placed on the skin of the thorax. There are no disposables. Uscom permits portable (& battery operated) noninvasive monitoring of cardiac parameters. An internal hard drive permits data storage.	Provides periodic (noncontinuous) measurement of cardiac output by Doppler ultrasound. There are two techniques used to acquire the Doppler signal with different sites on the thorax to place the transducer: 1. Aortic technique (suprasternal notch) 2. Pulmonary technique (left side intercostals spaces) Parameters displayed are: • Cardiac output / index (CO / CI) • Stroke volume / index (SV / SVI) • Heart rate (HR) • Systemic vascular resistance (SVI) • Peak velocity (Vpk) • Mean pressure gradient (Pmn) • Velocity time integral (vti) • Minute distance (MD) • Normalised ejection time (ET%) • Flow time / Flow time corrected (FT / FTc) • Stroke volume variation (SVV) • Systemtic vascular resistance / index (SVR / SVRI) • Stroke work (SW) • Cardiac power (CPO)	No contraindications identified. Aquisition of a correct signal is dependent on how the clinician positions and handles the transducer.	Uscom 1A has a fluid optimization protocol that utilises SV, SVI and FTC and prompts fluid challenges with 200 ml colloid fluid or 500 ml crystalloid fluid until the rise in SVI is < 10%.

9 Trials in progress

We identified three randomised trials in progress:

The Goal-directed Resuscitation in High-risk Patients Undergoing Cardiac Surgery (GRICS) study is investigating whether GDT in high-risk patients using the LiDCO*rapid* device, compared to standard care, reduces complications after cardiac surgery. The primary outcome measure is a composite of death or major postoperative complications and secondary outcome measures include duration of ICU stay and hospital stay. The target accrual is 144 patients and the study is expected to complete in December 2013.

Source: http://clinicaltrials.gov/show/NCT01470976

The optimisation of peri-operative cardiovascular management to improve surgical outcome (OPTIMISE) study is comparing GDT based on arterial waveform analysis versus standard care in patients undergoing major abdominal surgery. The trial has a target accrual of 726 patients and completed in May 2013. Patients in the intervention group receive also an infusion of dopexamine (0.5 µg/kg/min). Patients will be followed up for 30-day morbidity and mortality and 180-day mortality.

Source: http://www.controlled-trials.com/ISRCTN04386758

A multicentre randomised controlled trial has initiated in Spain with planned accrual of 840 high risk patients undergoing surgical procedures under general anaesthesia. The trial compares CardioQ-ODM guided fluid therapy with fluid therapy based on arterial pressure, temperature or urine output. The primary outcome measure is post-operative short term complications and secondary outcome measures are length of hospital stay and morbidity and mortality at six months after hospital discharge. The study closed early after accrual of 450 patients due to European-wide withdrawal of hydroxyethyl starch under the recomendations from the PRAC Committee from the European Medicines Agency (EMEA). Results based on 450 patients are anticipated by June 2014.

Source: http://www.controlled-trials.com/ISRCTN93543537 , also personal correspondence with the Principal Investigator, Prof. José M. Calvo Vecino.

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