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Optimisation of Fluid Therapy in Colorectal Surgery

Dr Sanket Srinivasa MBChB

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery at the University of Auckland, 2011
Abstract

Fluid administration is an important aspect of perioperative care in colorectal surgery. It has been largely guided by experimental evidence from the 1950s and extrapolated observations from injured soldiers during the Korean and Vietnam War. Recent improvements in perioperative care have led to renewed scrutiny of perioperative fluid management and challenged conventional wisdom with regards to the ideal quantity of fluid to be administered for patients undergoing colorectal surgery.

Chapter one introduces this topic with discussion of optimised perioperative care, fluid and electrolyte physiology, composition of intravenous fluids and their clinical implications. It discusses the history of fluid therapy and concludes that avoidance of fluid overload -fluid restriction– and individualised fluid therapy are considered as ideal fluid regimens in colorectal surgery, thus outlining the direction of the rest of the thesis- comparison of the two and exploring their place within the perioperative environment.

The prevalent heterogeneity in perioperative care and its influence on fluid administration is demonstrated in chapter two. Chapter three explores the feasibility of intraoperative fluid restriction and establishes a baseline for future comparative studies whilst also showing an important association between increasing fluid amounts and adverse clinical outcomes. Chapter four shows interest and equipoise concerning the use of individualised fluid therapy in clinical practice. It also demonstrates that the Oesophageal Doppler Monitor (ODM) is the most favoured instrument to conduct individualised fluid therapy. Chapter five is a systematic review of the methodology of the published trials exploring ODM-guided fluid therapy in
colorectal surgery. It outlines the methodology and limitations of prevalent evidence and allows for the design of prospective studies.

Chapter six is a prospective study of individualised fluid therapy in rectal surgery. Chapter seven is a prospective, randomised trial of individualised fluid therapy versus fluid restriction in patients undergoing colectomy within an otherwise optimised perioperative care environment. The prospective studies show that individualised fluid administration and fluid restriction provide equivalent outcomes in an otherwise optimised environment. The findings of this thesis have important scientific and clinical implications which are discussed in chapter eight and nine.
Dedication

Any accomplishment of significance is possible only with the support of others. This thesis, the work it represents and the time spent is dedicated to my family.
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1. Introduction

_The practice of surgery is the assumption of complete responsibility for the welfare of the patient._

**Francis D. Moore** (1913–2001), Moseley Professor of Surgery, Harvard Medical School and Chief of Surgery, Peter Bent Brigham Hospital, Boston, Massachusetts

There are approximately 234 million major surgical procedures performed worldwide every year. (1) A successful outcome from surgery is dependent on a technically proficient operation as well as optimised perioperative care, both of which necessitate an applied knowledge of the scientific principles of surgery. Whilst surgery provides obvious benefits, the long term advantages are preceded by an initial period of morbidity and prolonged convalescence, especially in colorectal surgery. This morbidity has a significant physiological basis.

1.1 The physiological impact of colorectal resection

The metabolic response to surgical trauma is governed by multiple complex and redundant biological systems. (2, 3) These include neuro-endocrine mechanisms as well as local and systemic pro-inflammatory cytokine release. (2, 3) Within surgical settings, the excessive release of pro-inflammatory cytokines has been correlated to adverse oncological outcomes, increased morbidity, delayed convalescence and post-surgical fatigue. (4-7) These physiological and clinical changes are of a profoundly greater magnitude in colorectal resection when compared to procedures of similar duration performed on comparable populations. (8, 9)

Major colorectal surgery is required for treatment of malignant or benign pathology and requires resection of the affected component with subsequent
anastomosis if possible. It is often undertaken in elderly patients who suffer from multiple health problems and is associated with significant post-operative morbidity and a prolonged recovery process that can affect patients well beyond their hospital stay.\(^{(10, 11)}\) The normal recovery process is manifested as post-surgical fatigue and has been shown to persist for up to three months following even an uncomplicated course.\(^{(12)}\) The clinical consequences and metabolic magnitude of colorectal surgery have been ascribed, in part, to excessive pro-inflammatory cytokine release after injury.\(^{(13)}\) This has both systemic and local peritoneal components.\(^{(13, 14)}\)

Previous studies have demonstrated the relationship between cytokine-mediated post-surgical inflammation and adverse clinical outcomes specifically in colorectal surgery.\(^{(14)}\) Paddison et al. also demonstrated a correlation between peritoneal inflammation and post-surgical fatigue.\(^{(6)}\) As a consequence, a significant body of work has centred upon trialling metabolic interventions to decrease post-surgical inflammation to improve outcomes after colorectal resection.\(^{(15, 16)}\) It has been shown that dampening the post-surgical inflammatory response using preoperative glucocorticoid administration, as an empirical anti-inflammatory measure, decreases pro-inflammatory cytokine release with corresponding decreases in hospital length of stay and complications.\(^{(17)}\) A greater understanding of the metabolic response to surgical trauma has led to significant improvements in perioperative care in recent history.

### 1.2 Optimised perioperative care

Modern perioperative care in colorectal surgery aims to decrease post-surgical inflammation and minimise end-organ dysfunction.\(^{(17-19)}\) This can be achieved through the simultaneous implementation of evidence-based strategies in the perioperative period and has resulted in accelerated recovery and decreased
complications. These strategies have often been packaged into standardised protocols in an effort to ensure that clinical implementation remains homogenous for all eligible patients. These are called Fast-Track or Enhanced Recovery After Surgery (ERAS) protocols. The concept of coordinated delivery of optimised perioperative care was pioneered by Henrik Kehlet in Denmark and is an area of increasing interest worldwide. There are numerous components to these perioperative care pathways which act both additively and synergistically.

1.2.1 Components of optimised perioperative care

These are outlined below in sequence from the preoperative to postoperative period.

1.2.1.1 Preoperative

Patients are seen preoperatively in an outpatient setting where they are presented with detailed information regarding the operation and post-operative period. Stoma education and goal-setting are carried out and a tour of the ward is conducted to familiarise patients with inpatient settings and decrease anxiety. Nutritional assessment is performed using appropriate tools and, if necessary, preoperative nutritional supplements are provided. Medical optimisation is undertaken with the assistance of anaesthetists and particular attention is given to preoperative smoking and alcohol cessation. Some authors have also begun to explore the concept of preoperative cardiovascular exercise programs – so called prehabilitation – to build physiological reserve. Patients are usually admitted on the day of surgery with avoidance of bowel preparation. Bowel preparation has been implicated in causing electrolyte disturbances and may lead to increased rates of anastomotic leakage, though its use in rectal surgery specifically is still supported.
Fasting is avoided and patients are given preoperative carbohydrate supplement drinks as these have been shown to decrease post-operative hyperglycaemia, insulin resistance and catabolism and may decrease complications. (29)

1.2.1.2 Intraoperative

Preoperative sedatives and anxiolytics are avoided and antibiotics are administered prior to induction of anaesthesia. A thoracic epidural is placed and activated preoperatively with a combination of local anaesthetic and opioid. This has been shown to attenuate the neuro-endocrine response to surgery and decrease the duration of paralytic ileus and may be beneficial with regards to oncological outcomes. (15, 30, 31) Epidural analgesia is normally continued for at least 48 hours postoperatively. Non-opioid analgesia is preferentially used.

Perioperative hypothermia is avoided by active warming and increasingly, laparoscopic techniques are being favoured for surgical intervention. (32) Laparoscopic colorectal resection has been investigated both independently and in this setting. (33-36) Transverse incisions have also been shown to be of benefit in some settings. (37) Preoperative glucocorticoids have been shown to provide benefits in short term recovery but have not been universally adopted. (17, 38) Intraoperative fluid therapy – the focus of this thesis, is a contentious area with centres adopting either fixed volume regimens or Goal-Directed Fluid Therapy (GDFT). (21)

1.2.1.3 Postoperative

Prophylactic insertion of drains and nasogastric tubes is avoided unless specifically indicated. Early feeding is commenced as this has also been shown to decrease post-operative catabolism. (39, 40) Simple analgesia and antiemetics are
prophylactically administered. In-dwelling catheters are removed early to decrease infectious complications and encourage mobilisation.(41) Supra-pubic catheters may be used instead of urethral catheters in rectal resections.(42) Minimal intravenous fluid is administered postoperatively.(43) Some pharmacological agents have shown benefit in decreasing the duration of postoperative ileus.(30)

Early mobilisation, with an emphasis on upright posture, is encouraged as it has been shown to improve pulmonary function and decrease skeletal muscle wasting.(44) Thromboembolic prophylaxis is mandatory unless specifically contraindicated. Nutritional supplements are also administered postoperatively for caloric replacement to attenuate negative nitrogen balance.(45) Pre-defined discharge criteria are used and patients are followed up in the community closely in the early postoperative phase and may be seen in an outpatient clinic within the first ten days after discharge where skin wounds and histology are reviewed.

1.2.2 Ongoing developments in optimised perioperative care

The principles mentioned above represent the current knowledge base regarding perioperative best practices. However, this is not a static field. Optimised perioperative care represents a template upon which continual advancements are possible and new interventions can be trialled.(46) These include advancements in surgical technique, alternative methods for management of symptoms such as pain and nausea, and metabolic manipulation of the surgical stress response.

The role of laparoscopy within the enhanced recovery context is still being defined.(47, 48) Natural orifice techniques are currently in their infancy but could potentially limit the systemic inflammatory response from surgery further with consequent implications for other aspects of care such as fluid management.(49) The role of epidural analgesia is also being questioned as is the role of non-steroidal
analgesia with concerns over potential detrimental impacts on anastomotic integrity for the latter.(50, 51) There is a significant body of research exploring alternative methods of providing analgesia within this setting.(15, 52) Similarly, preoperative glucocorticoids have also shown benefit in reducing morbidity after major abdominal surgery, whilst the potential benefits of other inflammatory modulators such as statins deserve further investigation.(17, 53, 54)

Other endeavours to decrease morbidity may also be integrated into optimised perioperative care protocols. These could include strategies to improve communication and teamwork, reduce surgical site infections or determine standardised criteria for patient expectations.(55-59) Therefore, it is important to acknowledge that perioperative care is in a state of flux with individual aspects warranting further scientific enquiry.

1.2.3 Uptake of optimised perioperative care

Optimised perioperative care has been shown to be efficacious locally and internationally.(20, 60) It has also been demonstrated as being cost-effective.(61) Interested individuals are also rapidly expanding the scope of ERAS by trialling multiple interventions.(62) However, it is yet to achieve global penetrance. Whilst considered routine in parts of Europe, ERAS protocols have not gained widespread acceptance in America and Australasia.(24, 63) Previous work has shown that important aspects of perioperative care, such as postoperative fluid management, are left to the most junior members of the surgical team who often have minimal knowledge of the subject.(64) Moreover, in another recent study, it has been demonstrated that only six percent of published abstracts at the Royal Australasian College of Surgeons’ Annual Scientific Congress were concerned with perioperative care.(65) A subsequent study of colorectal surgical research across America,
Europe and Australasia also demonstrated minimal research in perioperative care as determined by quantity and proportion of abstracts within prominent colorectal meetings. (66) Therefore, there is a dearth of both uptake of optimised perioperative care and perioperative care research in Australasia and globally.

A meta-analysis of the published randomised trials has demonstrated that ERAS protocols decrease hospital length of stay and complications. (20) Other evidence has suggested that patients are satisfied with this model of care. (67, 68) However, the published studies have not been able to demonstrate which specific interventions provide the clinical benefits seen. Some of the proposed benefits of individual components have not been demonstrated when independently tested in randomised trials. (69) A previous study demonstrated that the only predictors of day-stay within the Middlemore Hospital ERAS protocol were the patient’s preoperative comorbidities and the occurrence of postoperative complications. (70) This seems to imply that it is the additive and synergistic effects of the individual interventions at a metabolic level that provide the clinical benefits seen. Importantly, individual aspects of perioperative care are currently in a state of flux with multiple, seemingly contradictory schools of thought. This is particularly true with perioperative fluid administration. (71, 72)

1.3 Fluid and electrolyte balance

1.3.1 Body water and electrolytes

As a percentage of total body weight, 60% of the human male is composed of water. Due to the comparatively greater proportion of anhydrous adipose tissue in the female, 55% of the female body weight consists of water. If the round number of 60% is considered for ease of calculation, total body water (TBW) is distributed between the intracellular (40%) and extracellular space (20%). The extracellular fluid
(ECF) is further divided into interstitial fluid (ISF) (16%) and plasma volume (PV) (4%). These relationships are depicted in Figure 1. Transcellular fluids within the peritoneal, synovial, cerebrospinal and intraocular spaces are also present. These comprise a comparatively smaller proportion of TBW and are not generally included when discussing body water compartments.

**Figure 1**: Body water compartments

![Body Water Compartments Diagram]

- **TBW**: Total body water; **ICF**: Intracellular fluid; **ECF**: Extracellular fluid; **ISF**: Interstitial fluid; **PV**: Plasma volume

The main cation within intracellular fluid (ICF) is potassium (K⁺), whilst the main cation within the ECF is Sodium (Na⁺). The electrical neutrality of the ICF is maintained by K⁺ and the negative charges exerted by intracellular proteins and bicarbonate ions. Correspondingly, the integrity of the ECF is maintained by the concentration of Na⁺ and bound anions (e.g. chloride, bicarbonate). Transport across the cell membrane is via either simple or facilitated diffusion or mechanisms of active transport. The latter is dependent on the Na⁺K⁺ATP-ase energy dependent
pump which extrudes Na\(^+\) and chloride and maintains a Na\(^+\) gradient across the cell membrane. Ion-specific channels and aquaporins have also been described in contributing to transmembrane transport.(73) The electrochemical gradient across the cellular membrane is governed by the Gibbs-Donnan equilibrium.(74)

ISF and PV are divided by capillary endothelium or arterial/venous walls as appropriate. The Gibbs-Donnan equilibrium is also applicable to ionic shifts across capillary walls due to the presence of anionic plasma proteins in the PV. The capillary endothelium is permeable to small ions but comparatively impermeable to larger molecules, though there are considerable differences between individual tissues.

The main mechanism of fluid movement is diffusion through intercellular pores, which regulate the passage of molecules based on size and electrical characteristics. Fluid movement across this interface is dictated by the Starling equation and is thus dependent upon the net pressure vector when hydrostatic pressures and colloid osmotic pressure in the ISF and PV are accounted for. Movement is also dependent on membrane pore numbers and size, which are mathematically accounted for by the capillary filtration coefficient.(75) In health, this leads to net movement out of the PV into the ISF with a return into the PV via the lymphatic system.(76) Some plasma proteins including albumin also leak from the PV to the ISF at a steady rate in healthy states and may return via the lymphatic system and the thoracic duct.(77)

1.3.2 Water and sodium homeostasis

The body maintains both fluid and electrolyte balance through the actions of multiple organs including the kidney, adrenal glands, pituitary gland, hypothalamus as well as other neural regions and systemically located receptors. In this context,
Na\(^+\) assumes more importance as osmolality is more dependent on Na\(^+\) as compared to K\(^+\). As Na\(^+\) is the major cation in the ECF, changes in the concentration of Na\(^+\) thus lead to alterations in ECF volume. Homeostasis is maintained primarily through thirst mechanisms, the secretion of anti-diuretic hormone (ADH), which regulates volume, and activation of the Renin-Angiotensin-Aldosterone-System (RAAS).

Thirst is stimulated by the detection of an increase in osmolarity of greater than two milliosmoles by osmoreceptors – the thirst threshold. A decreased volume of ECF along with decreased arterial blood pressure is also detected by arterial baroreceptors leading to thirst. Angiotensin II (discussed below) stimulates thirst by acting directly on the periventricular neural regions and a dry mouth or dry mucous membranes of the oesophagus also stimulate thirst. These mechanisms work in conjunction with the secretion of ADH, which is released following similar stimuli.

ADH is a nonapeptide secreted by the posterior pituitary gland. It increases the reabsorption of water by acting on the V2 receptors in terminal portion of the distal tubule and the collecting ducts of the nephron. ADH acts to cause cytoplasmic vesicles containing water channels, such as aquaporin-2, to fuse with the luminal membrane increasing water permeability. ADH is secreted in response to increased osmolarity of the ECF as sensed by osmoreceptors in the hypothalamus in the periventricular organs outside the blood brain barrier. A loss of PV (e.g. in haemorrhage) also leads to the release of ADH due to decreased stimulation of atrial stretch receptors and arterial baroreceptors as well as activation of arterial chemoreceptors and release of angiotensin II. The opposite changes occur in the presence of water excess and secondary decreased osmolarity in otherwise healthy states. The concentration of Na\(^+\) is also inherently linked to regulation of water and
thus to ADH. ADH itself increases Na\(^+\) reabsorption in the thick ascending loop of Henle and collecting ducts. It is also known to regulate arterial pressure via its actions on the V1a receptor which regulates vascular smooth muscle tone.

Na\(^+\) concentration, and thus ECF volume, is monitored indirectly by the stretch receptors in the central veins and atria which dynamically assess central venous volume. This information is carried via the vagus to the hypothalamus and the cardiovascular centres in the brainstem. Baroreceptors located in the carotid sinus and aortic arch also regulate ECF if PV is depleted and systemic arterial blood pressure is decreased. Granular cells in the juxtaglomerular apparatus detect changes in renal perfusion pressure and relay this information to the neural cardiovascular centres. The consequences of these afferent impulses are largely actioned by the kidney.

The kidney autoregulates its glomerular filtration rate via sympathetic input and release of adrenaline from the adrenal medulla. Na\(^+\) and water reabsorption are also influenced by changes to the variables governing the Starling equation at the interface between peritubular capillaries and luminal fluid. The granular cells of the juxtaglomerular apparatus release renin and activate the RAAS in the presence of decreased arterial blood pressure; increased sympathetic stimuli acting on β adrenoreceptors or decreased rate of fluid across the distal tubule. The end-product of the RAAS is angiotensin II and this stimulates thirst, increases Na\(^+\) reabsorption in the nephron and has vasopressor properties including the constriction of glomerular arterioles as a negative feedback mechanism. These changes favour Na\(^+\) retention and increase ECF volume correspondingly.

Angiotensin II acts on the periventricular neural centres to increase secretion of ADH and adrenocorticotropic hormone (ACTH) and stimulates the secretion of
Aldosterone from the adrenal cortex. Angiotensin III and Angiotensin IV have also been described.\(^78\) There is some debate as to whether these are physiologically unique compounds or whether they are simply breakdown products of Angiotensin II with biological effects as Angiotensin III has shown 100% aldosterone-stimulating activity.\(^79\)

Aldosterone is also stimulated by ACTH release from the anterior pituitary gland and an increased concentration of plasma potassium. It promotes \(\text{Na}^+\) reabsorption via active epithelial sodium channels of the collecting ducts thereby stimulating transepithelial transport; by increasing synthesis and insertion of the \(\text{Na}^+\)-\(\text{K}^+\)-ATPase pump into cellular membranes and by upregulating the Krebs cycle. \(\text{Na}^+\) concentration is also regulated by other mechanisms such as renal prostaglandin synthesis, the kallikrein-kinin system, inhibitors of \(\text{Na}^+\)-\(\text{K}^+\)-ATPase and various natriuretic peptides.

### 1.3.2.1 Brain Natriuretic Peptide (BNP)

BNP was first isolated from the porcine brain and was subsequently found to be most abundant within cardiomyocytes of the ventricles.\(^80\), \(^81\) It is also secreted from the atria in lesser quantities.\(^82\) The biologically active form is derived from enzymatic cleavage of Pre-Pro-BNP to Pro-BNP to BNP. It is synthesised by cardiomyocytes in response to ventricular wall stress or ischaemia and exerts its actions via membrane-bound natriuretic peptide receptors.\(^83\) BNP induces vasodilation, natriuresis and diuresis to compensate for pressure or volume overload.\(^83\) It has permissive effects on myocardial relaxation and opposes the actions of the RAAS.\(^84\)

BNP levels in blood are a proxy for left ventricular dysfunction, which is particularly important as left ventricular dysfunction is asymptomatic in up to 50% of
individuals. (83, 85) Previous authors have postulated that BNP levels consist of a baseline “dry” component and a pathological “wet” component reflecting the degree of fluid overload. (83) In patients with volume overload, appropriate treatment causes a drop in BNP levels over a 24 hour period. (86) These observations have led some authors to propose that fluid balance in patients with cardiac disease should be guided by levels of natriuretic peptides to decrease ventricular wall stress. (87)

BNP levels may also be influenced by inflammatory states. (84) BNP has been shown to be increased in animal models of endotoxaemia with direct upregulation of the BNP gene by lipopolysaccharide. (88) Within a setting of septic shock, BNP has been shown to be a superior proxy of cardiac impairment compared to atrial natriuretic peptide. (89) The release of pro-inflammatory cytokines such as interleukin-6 (IL-6) have also been shown to directly contribute to BNP release and thus BNP may also be influenced by the magnitude of inflammation. (90, 91) Preoperative BNP measurements have also been shown to be an accurate predictor of early and late adverse events postoperatively in a meta-analysis of studies in non-cardiac surgery. (92)

1.4 Overview of fluid and electrolyte changes in surgery

Surgical trauma and perioperative interventions influence salt and water homeostasis considerably. Insensible losses, exacerbated by anxiety, can cause a fluid deficit though this has been shown to be often overestimated. (71) There may be a depletion of ECF and electrolyte derangement from preoperative fasting and the use of bowel preparation, which may be somewhat attenuated by the avoidance of prolonged fasting and administration of preoperative carbohydrate supplements. (27, 29, 93, 94) Drugs used in the perioperative period for anaesthesia,
as well as regional anaesthesia techniques such as epidurals, can cause vascular redistribution, vasodilation and fluid shifts.(95)

The fluid and electrolyte changes in response to surgery are described later but include a conservation of water and Na\(^+\) and their sequestration within the ECF through the actions of mediators described above. There has been considerable debate about the shift of fluid from the PV to the ISF and also to the theoretical “third space.”(71) This has been postulated to be either an intraluminal space (i.e. within the GI tract) or a non-functional portion of the ECF. However, attempts to quantify the third space have been inconclusive with some authors suggesting that a theoretical third space does not exist.(71) Instead, fluid shifts occur from the PV to the ISF, which can become pathological in larger amounts as lymphatic clearance is overwhelmed.(71)

Surgical trauma itself induces an inflammatory reaction and increases capillary permeability for leucocyte extravasation.(3, 96) This also causes a transfer of fluid from the PV to the ISF.(97) Previous work has also shown that the transcapillary leak rate of albumin increases up to threefold postoperatively due to both surgical trauma and fluid infusions.(77, 98) This leads to increased colloid osmotic pressure in the ISF encouraging the accumulation of fluid, whilst the resultant low intravascular volume leads to further salt and water retention.(97) Conversely, decreased oral intake and losses from stomata or fistulae lead to fluid deficits. Critically ill patients have been shown to have a deficit in intracellular water whilst conserving water in the ECF to display positive fluid balance overall.(99) Therefore, physiological and circulatory support needs to be provided as appropriate with the use of intravenous fluids.
1.5 Intravenous fluids

Intravenous fluids are a medication, which is prescribed when enteral intake is either not possible or insufficient to compensate for sustained or ongoing losses. Intravenous fluids can be broadly categorised into either crystalloids or colloids with differences in composition, pharmacokinetics and physiological properties.

1.5.1 Crystalloids

These are solutions of small organic molecules or inorganic ions dissolved in water. The composition and distribution characteristics of commonly used crystalloids is as per Table 1. The most common solutes are sodium chloride or glucose. Other solutes such as magnesium, lactate, potassium may also be present to replicate plasma composition as closely as possible. Such solutes are known as either balanced or physiological solutions. Isotonic solutions such as normal saline expand the ECF whilst hypotonic solutions (e.g. dextrose saline) distribute evenly across the ICF and ECF. The crystalloids used in the experiments detailed in this thesis are discussed below.

Table 1: Composition of commonly used crystalloid solutions as compared to plasma

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Normal saline</th>
<th>Dextrose Saline</th>
<th>Plasmalyte™</th>
<th>Ringer's Lactate</th>
<th>Hartmann's Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mmol/L)</td>
<td>135–145</td>
<td>150</td>
<td>30</td>
<td>140</td>
<td>130</td>
<td>131</td>
</tr>
<tr>
<td>Cl (mmol/L)</td>
<td>95–110</td>
<td>150</td>
<td>30</td>
<td>98</td>
<td>109</td>
<td>111</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>3.5–5.2</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>HCO₃ (mmol/L)</td>
<td>24–32</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Ca (mmol/L)</td>
<td>2.1–2.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
<td>4</td>
</tr>
<tr>
<td>Mg (mmol/L)</td>
<td>0.7–1.0</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>3.0–11.0</td>
<td>0</td>
<td>222.2 (40g)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Osmolality (mOsm/L)</td>
<td>275–295</td>
<td>300</td>
<td>282</td>
<td>294</td>
<td>273</td>
<td>274</td>
</tr>
</tbody>
</table>

Dextrose saline has been used as a postoperative maintenance solution for several decades since it avoids sodium overload and hyperchloraemic acidosis. (100) It does, however, cause hyponatraemia and has been described as causing
hypophosphataemia, though the latter is ascribed to haemodilution rather than a specific effect of dextrose saline.(101, 102) Some authors have proposed that dextrose saline is an unsuitable choice for postoperative fluid administration as the extracellular deficit is not able to be exclusively corrected without fluid loading the ICF.(103) However, these criticisms stem from a prevalent disagreement regarding the changes to the ECF postoperatively with the opposing theories of Moore and Shires, which are discussed later.(104-106) A recent randomised trial has illustrated that dextrose saline may cause transient hyperglycaemia though the clinical significance of this is uncertain.(107) A recent study in healthy volunteers has shown that a glucose load does not affect urinary excretion of water and sodium.(108) Importantly, since postoperative sodium overload is the more common clinical problem, with some authors proposing a teleological impairment in physiological adaptation to sodium overload, dextrose saline is the preferred crystalloid in the perioperative setting.(109)

Studies by Lobo and colleagues have established that saline solution is neither physiological nor ‘normal’.(110-113) In this text, saline is interchangeably referred to as normal saline in reference to clinically used nomenclature rather than any tacit misunderstanding regarding the unphysiological composition of saline solution. Previous work has shown that normal saline expands the PV by approximately 20% with the remainder of the fluid being sequestered in the ISF.(110, 114) Another study in healthy volunteers demonstrated that 60% of intravenous saline left the PV within 20 minutes of administration.(115)

Infusions of normal saline in healthy volunteers may require several days to be renally excreted and delay micturition.(116, 117) These effects are less pronounced with dextrose-containing solutions, which are excreted more readily.(118)
Randomised, cross-over studies comparing different crystalloid solutions have confirmed the same. (110, 114) These findings have been ascribed to the suppression of the RAAS and the compensatory transient actions of natriuretic peptides. (116) Renin release has been shown to be suppressed within 30–60 mins post-infusion of normal saline. (114, 116) Moreover, it has been previously shown that an increased chloride load – as would be expected with normal saline – decreases renal excretion of sodium by causing renal vasoconstriction and decreasing the glomerular filtration rate. (110, 119, 120)

Rapid infusion of large volumes of normal saline in healthy volunteers has been shown to cause nausea, abdominal discomfort, drowsiness and impair higher cognitive function. (121) Infusions of crystalloid solutions in healthy volunteers have also been shown to adversely affect pulmonary function and decrease functional residual capacity, though these changes were transient and did not change exercise capacity. (122) Nonetheless, the findings may be clinically significant in patients with minimal physiological reserve. The high chloride content of crystalloid solutions (especially normal saline) can lead to hyperchloreaemic metabolic acidosis, which is not seen with the administration of balanced crystalloid solutions. (123) These observations may be of clinical significance as evidenced by the study by Wilkes et al., which showed superior gastric mucosal perfusion in elderly surgical patients randomised to receive balanced solutions. (124) As a result, saline solution is not recommended for routine use as a crystalloid despite common use.

Plasmalyte™ has been proposed as a suitable crystalloid for intraoperative use. (125) Its ionic composition resembles plasma and it is not associated with hyperchloreaemic acidosis. In a randomised trial of patients undergoing major upper gastrointestinal surgery, those patients who received Plasmalyte™ instead of saline
displayed a more favourable metabolic profile with decreased chloride concentrations and a decreased base deficit.\textsuperscript{(126)} In a larger study of 90 patients undergoing renal transplantation, Plasmalyte\textsuperscript{TM} was shown to be superior to both saline solution and Ringer’s lactate with regards to similar laboratory parameters.\textsuperscript{(125)}

Therefore individual crystalloids are physiologically distinct and an awareness of their properties allows appropriate use in the perioperative setting. However, PV expansion can require large volumes of crystalloids due to their ubiquitous volume of distribution. This can predispose to tissue oedema and hence colloids can also be required for appropriate circulatory support.

\subsection{1.5.2 Colloids}

A colloid is any non-crystalline substance microscopically dispersed evenly throughout another one. Colloid solutions contain larger molecules dissolved in a carrier substance, which is often saline. Newer carrier solutions resemble plasma more closely and are known as ‘balanced’ colloids.\textsuperscript{(127)} The vascular endothelium is comparatively impermeable to colloidal solutions and thus a greater proportion of administered fluid remains in the intravascular compartment though this is context-specific where a greater proportion of administered colloids remain in the PV if there has been a loss in PV compared to healthy volunteers.\textsuperscript{(128, 129)}

Solutions in clinical use include the semisynthetic colloids such as gelatins, hydroxyethyl starch (HES) and dextrans as well as human plasma derivatives such as albumin and fresh frozen plasma. Gelatins are derived from hydrolysis of bovine collagen; Dextrans are made from enzymatic hydrolysis of sucrose; HES is a derivative of amylopectin, which is found in maize or potatoes. The molecular weight and size of colloids is variable and the size to weight relationship depends on the
molecular configuration, which is dictated by inter-atomic charges. The colloids vary considerably in their pharmacokinetic properties, volume of distribution and hence in their ability to cause plasma volume expansion. They also influence blood flow, coagulation and inflammatory parameters.

There is considerable literature comparing the efficacy of crystalloids and colloids in various situations. It is important to recognise that the different colloid solutions vary significantly in all the above characteristics. There are, in fact, considerable differences noted between the individual types of colloid products (e.g. 0.6 HES vs. 0.4 HES). A discussion of all these fluids is beyond the scope of this discourse and two colloid solutions used in the course of this thesis are described below.

1.5.2.1 Succinylated gelatine (Gelofusin™)

Gelatine fluids are all derived from bovine collagen and are either cross-linked, urea-linked or succinylated. Gelofusin™ is an iso-oncotic, polydisperse, succinylated gelatine solution weighing 30,000 kilodaltons. Succinylation of the gelatine molecule creates negative inter-atomic charges causing conformational change and increasing the size of the molecule thereby increasing its volume-expanding capacity. These characteristics allow Gelofusin™ to have a stated half-life of approximately three hours within the PV. Intravenous infusion allows Gelofusin™ to accumulate in the PV with the low molecular weight fraction also distributed in the ISF. Gelofusin™ is a polydisperse solution and is almost entirely renally excreted with the larger molecules requiring hepatic degradation prior to filtration. There is no evidence of tissue accumulation of Gelofusin™.

The safety profile of Gelofusin™ has been widely studied. Gelofusin™ has minimal effects on haemostasis overall as compared to other colloids.
Gelofusin™ has been reported to cause anaphylactic reactions in patients and is thought to be worse in this context when compared to other semisynthetic colloids. (134) The estimated incidence of this is 1:13000. Gelofusin™ has been previously shown to competitively inhibit renal tubular protein reabsorption and isolated case reports of acute renal failure have also been reported. (135, 136) However, Gelofusin™ is not regarded as nephrotoxic.

A recent study by Lobo and colleagues has evaluated the pharmacokinetics and physiological reactions to intravenous Gelofusin™ administration and compared these to both saline and Voluven™ (discussed below). (137) In a randomised study, one litre infusions of these intravenous fluids were administered to healthy volunteers. This study showed that 79% of administered Gelofusin™ was retained in the PV after one hour. Gelofusin™ produced hamodilution and decreased serum albumin though this was not different to comparable infusions of saline or Voluven™. Gelofusin™ administration decreased serum osmolarity and serum sodium whilst increasing the concentration of serum potassium, chloride and bicarbonate. There were no differences in either serum or urinary concentrations of sodium, potassium, chloride or bicarbonate between the three solutions although Gelofusin™ tended to produce less hyperchloraemic acidosis as a likely consequence of decreased chloride when compared to other solutions. This was determined by an increased concentration of serum bicarbonate upon Gelofusin™ administration. Gelofusin™ infusion suppressed the release of plasma ANP, aldosterone, renin and BNP in a statistically similar magnitude to the other administered solutions. (137) A similar study in patients undergoing cardiopulmonary bypass has, however, shown that Voluven™ maintains oncotic pressure better as compared to Gelofusin™. (138)
HES fluids are recognised by three numbers as listed above but will be referred to using the tradename from henceforth for ease of expression. The first number indicates the concentration of the carrier solution, normal saline in this case; the second is the mean molecular weight in kilodaltons and the third is molar substitution, which represents the proportion of glucose particles with hydroxyethyl residues attached. This value (e.g. 0.4, 0.5 0.6) lends HES products the colloquial terms of tetrastarches, pentastarches, hetastarches etc. Voluven™ is iso-oncotic and theoretically expands the PV in a 1:1 ratio. The colloids in Voluven™ are a polydisperse mass and the molecular weight is a mean of these particles. The pharmacokinetic relevance of this is that smaller particles are more easily renally excreted affecting the osmotic effectiveness of infused fluid on a continual basis.(139) The molar substitution is thought to be of most importance to the in vivo properties of all HES fluids including Voluven™ as it increases the solubility of the glucose particles, thereby inhibiting their enzymatic cleavage.(131) The other structural characteristic of HES solutions of physiological consequence is the pattern of hydroxyethylation. Hydroxyethyl groups are preferentially attached to either the C$_2$ or C$_6$ carbon atoms. Attachment to the C$_2$ atom prevents proper access to α-amylase as compared to the C$_6$ atom.(140) As a consequence, fluids with a high C$_2$/C$_6$ ratio produce a greater duration of haemodilution due to longer retention times in the PV.

As per the nomenclature, Voluven™ is a tetrastarch and is part of the third generation of HES solutions. It is derived from waxy-maize and has a C$_2$/C$_6$ ratio of 9:1. It is able to be more readily excreted from the PV and ISF as compared to other HES products. Pharmacokinetic data, as adopted from Westphal et al., are shown in Table 2.(131) Volunteer studies have shown high plasma clearance in both single
and multiple infusions indicating no significant plasma accumulation.\(^{(141, 142)}\) The clearance of Voluven™ has been shown to be significantly superior to other HES products in both volunteer studies and in one study in patients undergoing orthopaedic surgery.\(^{(143, 144)}\) It is important to note that the high PV clearance of Voluven™ does not adversely affect its capacity as a volume expander and many studies have shown comparable outcomes to other HES products which show greater PV accumulation.\(^{(145)}\) These volunteer studies are also supported by studies in a surgical setting and have shown that the incidence of itch – thought to be caused by tissue accumulation of colloid solutions – is also reduced in patients being administered Voluven™.\(^{(144-146)}\)

### Table 2: Voluven™ – Pharmacokinetic data

<table>
<thead>
<tr>
<th>Dose (g)</th>
<th>(C_{\text{max}}) (mg/mL)</th>
<th>Clearance (mL/min)</th>
<th>Infusion time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voluven™(^{(141)})</td>
<td>26.3</td>
<td>3.7</td>
<td>31.4</td>
</tr>
</tbody>
</table>

The clinical impact and safety profile of Voluven™ have been investigated in both \textit{in vitro} and \textit{in vivo} models. Voluven™ has been shown to induce a hypocoagulable effect of lesser magnitude compared to earlier products. In the surgical setting, despite usage of high doses of Voluven™, no adverse effects on coagulation have been reported.\(^{(146, 147)}\) Pooled analyses exploring Voluven™ use in patients undergoing major surgical procedures showed that the use of Voluven™ was associated with significantly decreased requirement for blood products.\(^{(148)}\) Early studies had raised the possibility of adverse effects on renal function with the use of Voluven™ and tetrastarches in general.\(^{(149, 150)}\) However, subsequent randomised studies in potentially vulnerable patients undergoing major surgery and phase four surveillance studies have alleviated these concerns.

Voluven™ has been demonstrated to have important anti-inflammatory effects. Studies of patients undergoing major abdominal surgery have shown that patients
receiving Voluven™ had lower levels of proinflammatory cytokines such as IL-6 and interleukin-8. Volta et al. have shown that Voluven™ is able to selectively inhibit matrix metalloproteinase-9 in vitro and in vivo in a study of patients undergoing colon resection. These effects have been proposed to be a consequence of direct influence on endothelial and neutrophil activation and adhesion and may be of clinical relevance since attenuating the post-surgical inflammatory response has been shown to improve outcomes. As mentioned above, Voluven™ has shown comparable volume-expanding properties to Gelofusin™ with similar effects on serum composition in studies undertaken in healthy patients and a similar study in abdominal surgery is currently being conducted.

1.5.3 Summary of intravenous fluids

The comparison between crystalloids and colloids is a contentious topic. Numerous trials and subsequent meta-analyses have been unable to provide a convincing answer to determine the superiority of one solution over another. This is further confounded by the differences in individual crystalloid and colloid solutions rendering any global comparison of crystalloids and colloids less generalisable. The most suitable fluid depends on the patient and the clinical situation. With no professional consensus, clinicians have resorted to prescribing intraoperative fluids as per their individual preference.

The above description of intravenous fluids has outlined their basic properties. Whilst the different fluids have been discussed in isolation, a considerable body of evidence exists which compares the relative advantages and disadvantages of these solutions in different settings. Moreover, the advent of balanced colloid solutions hold the promise of further optimising the composition of intravenous fluids. However, this thesis centres around the optimal strategy for perioperative fluid
administration with a focus on the ideal *quantity* of fluid. Therefore, the composition of these solutions must be considered alongside the quantity of their administration in the context of the metabolic changes in surgery for rational perioperative fluid management, which is discussed next.

1.6 Perioperative fluid administration – History

The therapeutic importance of intravenous fluids was first demonstrated through the work of O’Shaughnessy, Latta and others in the 1830s who reported successful treatment of the “black blood” of cholera by administration of large volumes of intravenous fluids to “restore its arterial qualities.” (156, 157) O’Shaughnessy proposed this treatment after only testing his “potion” on a dog and reporting “no ill effects.” Thomas Latta, William O’Shaughnessy and others recognised the circulatory deficit prevalent in affected patients and devised physiological solutions to be injected intravenously to compensate for luminal losses.

In the 1880s, the use of intravenous fluids began to gain traction for the treatment of haemorrhage and shock. (158, 159) Egerton-Jennings described a moribund patient suffering from antepartum haemorrhage in the courtyard outside the hospital for whom he could not find a donor for blood transfusion. He therefore successfully trialled an infusion of intravenous fluid until “signs of animation very rapidly appeared.” A similar result was noted in the context of shock and thus the role of intravenous fluids for resuscitation purposes began to be established.

The work of Koelliker in the 1850s and that of Sydney Ringer further emphasised the importance of the composition of intravenous fluids, especially the inorganic components. (160) Ringer wished to “ascertain the influence each constituent of the blood exercises on the contraction of the ventricle” and used the model of isolated...
frog ventricles as originally described by Carl Ludwig, the German physician and scientist. The ventricles failed to contract in saline solution until one morning when they continued to “beat well for more than four hours,” seemingly in 0.75% saline solution. As it turned out, Ringer’s laboratory assistant had prepared the saline solution using tap water from the New River Water Company instead of distilled water as on other occasions. Conversely, the ventricle grew “weaker and weaker” when placed in saline solution prepared with distilled water. Thus, Ringer concluded that the inorganic components introduced into the circulating fluid from tap water created an alkaline environment that was more physiologically conducive to cardiac function. This led to the creation of Ringer’s solution. Alexis Hartmann later adapted Ringer’s solution by adding sodium lactate to it to successfully treat infants with diarrhoea. (161, 162) This laid the foundations for the concept of “balanced solutions” in use today.

In 1888, Thomas Churton suggested published a case report concerning a patient with ‘scirrhus of the pylorus,’ who was successfully resuscitated with intravenous fluids. He remarked that “the success of transfusion of a so-called normal saline solution to replace the lost water and salts of the blood was more permanent than in cholera, where there is a poison; or in cases of haemorrhage and anaemia, where blood cells are also wanting” and postulated that with “…intravenous injection of a saline solution, or a mixture of such a solution with blood, strength might be obtained to endure or to rally after an operation (of any kind) from which some exhausted patients could not otherwise recover.” (163) Subsequently in 1905, Pringle et al. reported that ether anaesthesia caused urinary retention and oliguria beginning from the first half hour of complete anaesthesia. (164) They postulated that anaesthesia exercised a “most injurious effect on the general metabolism and condition of the patient.” (164) Perioperative
circulatory support with fluids thus began to be increasingly utilised though these were initially administered per rectum or subcutaneously. (165)

The continuous administration of intravenous fluids by “drip” in the surgical setting was proposed by Rudolph Matas in a series of case reports published in 1924. (166) He advocated the use of ongoing intravenous fluids perioperatively for surgical patients “when there is an urgent need of a prolonged prop to the circulation in the great emergencies or crises of surgical practice.” He also recommended the use of glucose-containing solutions rather than “decinormal so-called physiological salt solution.” In his opinion, glucose-containing solutions were “incomparably superior to all other methods of parenteral nutrition and medication” and were justified to “beset the precarious existence of the (surgical) patients under consideration.”

In 1936, Frederick Coller and colleagues demonstrated improvements in morbidity and mortality through the avoidance of pre-renal, renal failure by administering perioperative intravenous fluids. (167) In 1938, they recommended administration of saline for both maintenance and resuscitation purposes but later retracted these recommendations following their own observations of electrolyte derangement and post-operative pulmonary oedema. (168, 169) Nonetheless, the benefits of intravenous fluids per se were not in question and Coller recommended the administration of dextrose solutions instead. Interestingly, in 1911, the potential dangers of saline solution were expressed by Evans saying, “…the disastrous role played by the salt solution is often lost in light of the serious conditions that call forth its use.” (170)

An area of increasing scrutiny in the 1940s and 1950s was the changes in fluid and electrolyte physiology observed in the post-surgical setting. In 1949, Wilkinson et al. demonstrated that the excretion of Na⁺ and chloride was reduced for the first
six days after surgery and subsequently demonstrated that this was not due to reduced intake but an active mechanism of salt conservation.\(^{(171)}\) He also theorised that these changes coincided with the catabolic phase described by Cuthbertson without the latter being the cause of the electrolyte changes.\(^{(171, 172)}\) In 1950, Wilkinson et al. demonstrated that potassium was renally excreted in large quantities in the first 24 hours after surgery and proposed that this was due to intracellular depletion.\(^{(173)}\) Le Quesne and Lewis subsequently postulated three overlapping phases to salt and water preservation in 1953. They postulated a period of primary water retention in the first 24 hours postoperatively; early sodium retention also within the first 24 hours and late sodium retention persisting for a several days postoperatively.

It was around this time that Francis D. Moore published his seminal article, “Bodily Changes in Surgical Convalesence.” This characterised the post-operative recovery process and underpinned the foundations for understanding the metabolic response to injury.\(^{(174)}\) In his study, he also described the relative oliguria on the day of surgery as well the dependence of total body water on the quantity of administered fluids during what he deemed the Adrenergic-Corticoid Phase. During the Corticoid withdrawal phase, he described a brisk diuresis to compensate for previous overloading. In the subsequent two phases, he described increases in total body water as a consequence of the anabolic processes restoring homeostasis by increasing lean, hydrous tissue in the body.

In his subsequent work on characterising patterns of water and electrolyte change in the post-surgical setting, Moore described that the response to surgical trauma included the preservation of water and Na\(^{+}\) by expansion of the ECF and proposed this to be a consequence of antidiuretic hormone from the posterior
pituitary gland based on supporting evidence from previous studies.(175-180) This was subsequently proven on bioassay.(181) Moore wrote that the “diminished excretory capacity for water should be borne in mind in prescribing postoperative fluids” as “efforts to increase urine volume by large infusions result only in the retention of a high proportion of the administered water” and thus recommended judicious use of perioperative fluids.

Moore’s contemporary, GT Shires described an opposite response to surgical trauma. In 1961, Shires demonstrated that the ECF volume decreased following surgical trauma due to internal redistribution of fluids and thus recommended that large quantities of intravenous fluids be administered to support the circulation.(105) He concluded that “many of the observed alterations in hormonal output, renal responses and compensatory efforts to correct extracellular fluid volume in the postoperative period can be ascribed to a progressive marked diminution in functional extracellular fluid incurred by the operative trauma itself.”(105) These findings were later found to be compromised by a methodological error as demonstrated by Roth in 1969.(182) Subsequent authors have demonstrated either unchanged or increased ECF volumes and the response of ECF to surgical trauma is not conclusively known.(183) Despite their conflicting findings, Moore and Shires published an editorial together in 1967 titled “Moderation.” In this, they suggested that the “objective of care is restoration of normal physiology and normal function of organs, with a normal blood volume, functional body water and electrolytes…” and cautioned against using set formulae just as Coller had warned in 1944.(184)

These laboratory studies coincided with clinical observations during the Korean war where improved survival was demonstrated upon administration of large quantities of fluids to injured soldiers.(185) Despite reports of post-resuscitation
pulmonary oedema as a result of over-enthusiastic administration of Ringer’s lactate in soldiers from the Vietnam war (186), these observations were also extrapolated to elective surgery. (182, 187) As a result the distinction between resuscitation and maintenance was lost. Subsequently, perioperative fluid administration often involved large quantities of fluid administered as maintenance fluid even in the absence of significant blood loss. These practices stemmed from the selective following of historical precedence as described above as well as concerns regarding preservation of urine output, maintenance of measurable proxies of cardiac output such as blood pressure as well as mitigating the effects of preoperative fluid deficits (e.g. from fasting, bowel preparation) and the vasodilatory effects of regional anaesthesia. (188, 189) Moreover, it is held by many that excessive fluid can be renally excreted efficiently without adverse consequences. (71, 190) Until the renewed emphasis on optimised perioperative care and accompanying scrutiny of perioperative fluid regimens, this practice was continued with consequent perioperative fluid imbalance. (191)

1.7 Perioperative fluid imbalance

Safe administration of intravenous fluid in the perioperative period requires avoidance of inadequate or excessive fluid administration – designated as fluid imbalance – as both have physiological and clinical consequences. (192)

1.7.1 Perioperative fluid deficit

Perioperative fluid deficits can cause circulatory inadequacy with systemic effects. At a cellular level, circulatory inadequacy can lead to decreased oxygen concentrations with a corresponding decrease in adenosine triphosphate for metabolic processes. Anaerobic metabolism is then preferentially used with the production of lactate and consequent acidosis.
Those patients who are preoperatively dehydrated as a consequence of fasting, insensible losses, or bowel preparation benefit from intravenous fluid. Inadequate fluid may lead to decreased preload and stroke volume. In extreme states, such as significant haemorrhage, this manifests as hypovolaemic shock. A fluid deficit also increases the viscosity of pulmonary mucus, thereby increasing the risk of atelectasis. Low PV may also affect blood rheology secondary to haemoconcentration and thus affect tissue perfusion as well as predisposing to a hypercoagulable state. Renal hypoperfusion may cause pre-renal, renal failure with oliguria. Inadequate ECF may lead to fluid shifts with a subsequent decrease in ICF. In the brain, neuronal shrinkage may also lead to seizures and brain damage. Low oxygen tension in surgical incisions may impair wound healing.

Since surgical trauma elicits a stress response with activation of the sympathetic nervous system, there is a neurogenic reduction in splanchnic perfusion secondary to vasoconstriction. This may be further exacerbated in the presence of an inadequate circulatory volume. This hypoxaemia can lead to splanchnic hypoperfusion and acidosis. Some authors have suggested that this can influence intestinal permeability with bacterial translocation and the development of the systemic inflammatory response syndrome. Moreover, the integrity and perfusion of the gastric microcirculation is difficult to measure and individuals may have occult hypovolaemia despite normal arterial blood pressure. Concerns regarding these sequelae have led authors to propose that a greater quantity of fluids should be administered in the perioperative period, though perioperative fluid excess is also associated with significant harm.
1.7.2 Perioperative fluid excess

Excessive administration of intravenous fluids in the perioperative setting can lead to numerous adverse consequences. Excessive fluids cause cellular swelling with cytosolic acidification and defective phosphorylation resulting in impaired intracellular signalling.\(^{(202, 203)}\) Cellular swelling also leads to the release of pro-inflammatory cytokines potentiating organ dysfunction.\(^{(202, 203)}\)

Although fluid administration increases cardiac preload – thereby improving cardiac output – excessive fluids impair cardiac contractility as myocardial myocytes are stretched beyond their optimal eccentric length for contraction.\(^{(204)}\) This causes suboptimal ventricular muscle contraction and is commonly depicted as the “plateau” phase of the Starling myocardial performance curve as shown in Figure 2. As a result, tissue perfusion is impaired. Moreover, intravenous fluids can also cause haemodilution impairing efficient oxygen delivery and causing tissue hypoxia.\(^{(188, 205)}\) The increased systemic blood pressure due to excessive intravenous fluids also increases capillary hydrostatic pressure. Within the pulmonary circulation, this leads to increased transudation of fluid into alveoli. This may ultimately lead to pulmonary oedema and impair pulmonary gas exchange further impairing oxygen delivery to the tissues as well as increasing the risk of pneumonia.\(^{(97)}\) Increased capillary pressures within the systemic circulation may also disrupt the Starling equilibrium and lead to fluid deposition in the ISF manifested as peripheral oedema.\(^{(188)}\)
Excessive fluids impose greater functional demands on the kidneys, especially as anaesthetic agents can depress glomerular filtration. Fluid overload may also cause a renal compartment syndrome as kidney swelling is prohibited by the relatively non-distensible renal capsule. Intravenous fluids in excess quantities may also lead to gastrointestinal dysfunction. They can cause submucosal oedema with mucosal hypoperfusion and predispose to paralytic ileus with increased nausea and vomiting. Increased submucosal oedema in colonic anastomoses has been shown to lower anastomotic burst pressures in a murine model. Excessive fluids may also cause splanchnic oedema and ascites with increased intra-abdominal pressure which is associated with increased gut permeability and intestinal failure as a result of decreased mesenteric blood flow.

Patients who have undergone trauma resuscitation have been shown to have secondary abdominal compartment syndrome with hypoxia and acidosis. Acidosis has a negative inotropic effect on myocardial muscle and decreases responsiveness to administered inotropes whilst also impairing renal function. Subcutaneous fluid administration in tissue may decrease tissue oxygen tension and
influence wound healing adversely. Fluid loading may also lead to cerebral oedema and hyponatraemia. Fluid shifts between the ICF and ECF can occur secondary to the osmotic gradient created by different fluids administered and may lead to confusion and seizures. Intravenous fluids influence coagulation variably. It is important to acknowledge that the discourse above has drawn from studies conducted in both animal models and human studies with the latter being conducted in healthy volunteers and in patients not necessarily undergoing colorectal surgery. Nonetheless, they illustrate the important point that there are potentially systemic consequences of perioperative fluid overload.

1.8 Fluid administration strategies

1.8.1 Fixed volume strategies

With the increased emphasis on optimised perioperative care over the last decade, each aspect of perioperative practice has undergone renewed scrutiny. In accordance with this, the historic practice of liberal fluid administration in major abdominal surgery was challenged by a number of randomised trials evaluating ‘high’ versus ‘low’ fixed volume regimens.

1.8.1.1 Fluid restriction in major abdominal surgery – Randomised trials

Lobo and colleagues conducted a randomised trial of postoperative fluid restriction in 20 patients undergoing elective colectomy to investigate the influence of post-operative fluid restriction on gastric emptying as judged by dual isotope radionuclide scintigraphy. Patients were randomised to either at least three litres of intravenous crystalloid fluids and 154mmol of Na\(^+\) or less than two litres of intravenous crystalloid fluids and 77mmol of Na\(^+\) per postoperative day. They demonstrated that post-operative fluid restriction increased gastric emptying, lead to earlier resumption of bowel function and decreased complications and hospital...
length of stay. This physiological experiment demonstrated the effects of salt and water overload on gastric function.

Arkilic and colleagues conducted a randomised trial of conservative (8mL/kg/hr) versus “aggressive” (16–18mL/kg/hr) intraoperative crystalloid fluid therapy in 56 patients undergoing elective colon resection. No colloid solutions were administered in this trial. The authors hypothesised, and subsequently demonstrated, that supplementary crystalloid administration increased tissue oxygen pressure. They hence concluded that “aggressive” fluid administration is necessary to treat undetected hypovolaemia. Importantly, however, the authors did not report clinically significant secondary outcomes such as complications and, as they themselves acknowledged, they did not evaluate whether improved tissue oxygen pressure decreased wound infections.

Brandstrup et al. conducted a multi-centred randomised trial of perioperative fluid restriction in 172 patients undergoing elective colorectal resection. Patients were either randomised to a standard regimen or to a restrictive regimen aimed at preventing weight gain in the perioperative period. The authors demonstrated a significant difference in the volume of fluid administered with patients receiving restrictive fluid management experiencing significantly fewer complications – the primary outcome – and a trend towards decreased mortality. This was the largest trial evaluating perioperative fluid restriction and demonstrated statistically significant decreases specifically in cardiopulmonary and major complications. The authors concluded that “perioperative intravenous fluid therapy aiming at unchanged body weight reduces complications after elective colorectal surgery.”

Kabon et al. continued the work begun by the previous trial of Arkilic et al. and conducted a randomised trial evaluating the impact of high versus low volume
crystalloid infusions on wound infections in 253 patients undergoing elective colon resection. They hypothesised that supplementary crystalloid administration in the same volumes as administered in their previous trial would increase tissue oxygenation and thus reduce the rate of wound infections. However, they found no significant decrease in the wound infection rate between the two regimens and no differences in hospital length of stay. Other endpoints including complications were not reported and it is important to note that this study was underpowered for its primary endpoint of wound infections, as acknowledged by the authors themselves. Moreover, further analysis of fluid volumes administered in this trial and the previous study by Arkilic et al. suggests that the patients in this trial receiving supplementary crystalloid may in fact only have received adequate fluid to achieve normovolaemic status given the use of bowel preparation and when compared against existing guidelines for fluid administration.

Nisanevich et al. conducted a randomised trial comparing a restrictive and liberal intraoperative fluid administration regime in 152 patients undergoing major abdominal surgery. The primary endpoint was a combination of morbidity and mortality. Patients receiving liberal fluid management received a preoperative bolus of 10mL/kg/hr Ringer’s lactate followed by an intraoperative infusion of 12mL/kg/hr of Ringer’s lactate. Patients receiving restrictive fluid management received 4mL/kg/hr of Ringer’s lactate intraoperatively. Patients receiving restrictive fluid management were shown to have decreased weight gain and experienced decreased complications with earlier recovery of bowel function and decreased hospital length of stay. This study was unique in that it had a high proportion of patients with significant comorbidities, unlike the trial by Brandstrup et al., and was conducted in patients undergoing both colorectal and upper gastrointestinal surgery.
Mackay et al. conducted a subsequent randomised trial of postoperative fluid restriction in 80 patients undergoing elective colorectal resection to detect any differences in hospital length of stay. In this trial, all patients underwent intraoperative fluid restriction but were then randomised to either conventional or restrictive postoperative fluid administration. The postoperative fluid regimes were identical to those described by Lobo et al. This trial found no difference in bowel function, morbidity or length of stay between the two groups. The authors thus proposed the relatively greater importance of intraoperative fluid restriction in obtaining clinical benefit suggesting that excess postoperative fluids may be more easily renally excreted. Subsequent analysis has shown that both groups of patients received intraoperative fluid restriction and thus received considerably less fluid than in the trial by Lobo et al. Even those patients who were not fluid restricted postoperatively did not receive excess crystalloid as evidenced by weight changes. As a result, both groups of patients were in fact normovolaemic when the entire perioperative phase was considered with no clinically significant differences in fluid balance, thus explaining the apparent discrepancy when comparing this trial with Lobo et al.

Holte et al. from Denmark conducted a randomised trial of liberal (median: 5050mL) versus restrictive (median: 1640mL) perioperative fluid administration in 32 patients undergoing elective colonic surgery within an ERAS protocol. The fluid algorithms consisted of fixed rates of Ringer’s lactate and Voluven™ infusions. The authors reported improved pulmonary function as their primary outcome and oxygenation in patients receiving restrictive fluid administration though serum cardiovascular hormones suggested decreased physiological stress in patients receiving more fluids. Importantly, there were a greater number of complications in
patients being managed with perioperative fluid restriction. This was the first study to be conducted within an established ERAS protocol.

Gonzalez-Fajardo and colleagues conducted a study comparing postoperative fluid restriction in 40 patients undergoing abdominal vascular surgery. (218) The authors randomised patients to either 2500mL or 1500mL of intravenous fluids per day postoperatively. There was a non-significant trend towards decreased complications and no difference in recovery of bowel function but patients randomised to the restrictive regime had significantly shorter hospital length of stay. This paper was only available in abstract form and hence further details are unavailable.

Vermeulen et al. conducted a randomised trial of postoperative fluid restriction in 62 patients undergoing major abdominal surgery. (219) The trial was powered to detect differences in hospital length of stay. Patients were allocated to one of two groups with each group receiving identical fluid amounts as described in the trial by Gonzalez-Fajardo et al. (218) A combination of Ringer’s lactate and saline solution was used in this study. This trial was stopped after an interim analysis as the patients in the restrictive fluid group had a significantly longer length of stay and experienced more major complications. The authors thus concluded that postoperative fluid restriction was harmful in this cohort of patients.

McArdle et al. conducted a randomised trial of perioperative fluid restriction in 21 patients undergoing open abdominal aortic aneurysm repair to detect any difference in major complications. (220) The authors demonstrated significantly decreased cumulative fluid balance in patients being managed with restrictive fluid administration (Mean: 2570mL vs. 8242mL) and showed these patients to
experience fewer major complications and decreased hospital length of stay. This trial was also stopped after an interim analysis due to the clinical benefits seen.

WenKui et al. recently conducted a randomised trial of restricted perioperative fluid regimens in 299 patients undergoing surgery for gastrointestinal malignancy. (221) The primary endpoint of the trial was total complications. The premise of this trial was that patients were either randomised to a restrictive fluid regimen or to a restrictive fluid regimen with supplemental colloid administration as guided by postoperative serum lactate levels. Patients received a maximum of 25mL/kg of Ringer’s lactate solution with administration of supplementary 6% HES solution. One group received colloid boluses as guided by hourly measurements of serum lactate intraoperatively and less frequent measurements postoperatively whilst the control group received supplementary fluid on clinical criteria alone. The authors demonstrated that up to 28% of patients experienced tissue hypoperfusion as per serum lactate measurements and that supplementary fluid administration decreased total complications.

Futier et al. conducted a randomised trial of two different fluid regimens in 70 patients undergoing major abdominal surgery. Eligible operations included all surgery expected to last more than 60 minutes including colonic surgery, rectal surgery, hepatectomy and gastric surgery. Patients were randomised to either 6ml/kg/hr or 12ml/kg/hr infusions of crystalloids intraoperatively. Both groups also received boluses of colloid based on measurements from the Oesophageal Doppler monitor (see below). Within this heterogeneous cohort, the authors demonstrated that those patients who received more fluid had fewer complications and greater indices of oxygenation. The authors thus concluded that fluid restriction in this setting predisposes to hypovolaemia and leads to complications.
Abraham-Nordling et al. conducted a randomised trial of restricted versus standard fluid management in 161 patients undergoing colorectal surgery. All patients were managed within an enhanced recovery environment. Patients in the restricted group received a median of 3050mL of fluid on the day of surgery compared to 5775 ml in the standard group. These amounts included fluids given both in the intraoperative period and in the immediate postoperative period. Intraoperative fluid amounts were a median of 575mL in the restricted group and 2500 in the standard group and the total fluid amounts administered over the entire stay were not reported. The primary endpoint of the study was hospital length of stay and there were no differences between the two groups. However, patients in the fluid restriction group experienced significantly fewer complications.

Even though the body of evidence appears to be conflicting, the professional consensus has been that restrictive fluid regimens are superior to liberal fluid regimens in elective abdominal surgery. Fluid restriction was also demonstrated in one meta-analysis as leading to decreased complications. Some authors have stated that fluid restriction is in fact just an avoidance of perioperative fluid overload. A recent critical analysis of fixed volume strategies and fluid restriction has also highlighted important deficiencies in the current evidence base. The review by Bundgaard-Nielsen et al. has indicated that published evidence is compromised by heterogeneity in the definitions used for fluid regimens and periods of therapy (e.g. perioperative, intraoperative, postoperative) as well as differences in perioperative care. Lobo has proposed that the important condition to avoid is perioperative fluid imbalance – incorporating both too much and not enough fluid – and that the right amount of the correct type of intravenous fluid must be given at the right time. He has stated further that a weight gain of greater than 2–3 kg is probably clinically significant.
In a meta-analysis published by Varadhan and Lobo, they reclassified the arms of trials as per patients being managed in a state of 'balance' or 'imbalance' on the basis of administered fluid volumes and anticipated changes in weight.(192) They demonstrated that patients being managed in a state of fluid balance experienced fewer complications and a shorter hospital length of stay.(192) Therefore, although the avoidance of the historic practice of fluid overload is of benefit, the optimal fluid strategy may in fact involve physiologically grounded principles of fluid administration as recommended by Moore and Shires almost 50 years ago.(184) A prevalent theory around this was proposed in the 1980s.

1.8.2 Targeted fluid administration

In 1973, William Shoemaker and colleagues from the University of New York described physiological patterns in cardiorespiratory variables in surviving and non-surviving shock patients.(225) In this series, they demonstrated that survivors were characterised by more favourable indices of cardiac and circulatory function as measured by invasive means in intensive care settings. Subsequent work from the same group demonstrated the same in patients who had undergone major surgery(226) and thus they deduced that tissue hypoperfusion, prevalent from the intraoperative phase, was a key initiating event in the development of complications. Shoemaker thus concluded that the "values of normal unstressed persons are not necessarily the therapeutic goals for the postoperative shock patient" and proposed supranormal values as therapeutic targets for resuscitation and tested this hypothesis in a randomised trial.(227, 228)

Patients were randomised to monitoring by either pulmonary artery catheters or central venous pressure to achieve supranormal values in cardiorespiratory parameters.(226-228) These patients were compared to the control group who
received conventional haemodynamic management. Their results showed that patients randomised to the monitoring groups had statistically significantly decreased mortality when compared to controls. The authors postulated that increased monitoring had allowed them to compensate for the increased post-surgical metabolic demands in a dynamic way and showed that this was cost-effective. (228)

This work was supported and refuted by other studies. (229) Trials that showed no benefit were criticised for instituting management after the development of cellular dysfunction or organ failure, signifying the importance of timely treatment and the importance of optimising perfusion in the intraoperative period. (229) Following their initial study, however, the investigators wrote that “the protocol, defined by median values of survivors may be overly aggressive for elderly patients with limited capacity for physiological compensation…” (228) This hypothesis was further explored by a multicentred, randomised trial of 762 critically ill patients, which showed no benefit from supranormal fluid therapy. (230) A subsequent trial, conducted by Shoemaker’s group, randomising patients to either normal or supranormal indices as a therapeutic goal also showed no difference in outcome between the two groups except to show that those who achieved the stated goals in each group fared better. (231) This trial also showed that the strongest predictor of survival was age under 40. (231) This emphasised the concept that observed supranormal variables were a reflection of physiological reserve in individual patients rather than the goal. The therapeutic goal is one fundamental conceptual difference between the studies exploring supranormal optimisation and the concept of GDFT.
1.9 Goal-Directed Fluid Therapy

1.9.1 Definition

GDFT involves the administration of intravenous fluids and/or vasoactive drugs to optimise pre-defined, patient-specific proxies of tissue perfusion. The individual parameters used to guide therapy are usually measurable cardiac variables such as cardiac output and depend on the monitoring system used (discussed below).

1.9.2 Rationale

Global haemodynamic variables are thought of as indicative of the state of the microcirculation and have hence been extrapolated to determine the adequacy of tissue perfusion. However, arterial blood pressure does not correlate to circulating blood volume.(232) Cardiac output may also be significantly decreased without an accompanying change in blood pressure.(233) As a result, tissue hypoperfusion may occur without any appreciable change in conventionally measured systemic parameters of perfusion such as heart rate, blood pressure or urinary output. The body’s response to hypovolaemia includes autonomic vasoconstriction of the splanchnic circulation to provide adequate perfusion to the brain and heart. There is a 40% reduction in the splanchnic circulation following a 10–15% reduction in circulating blood volume.(234) Experimental evidence suggests that this regional hypoxia can remain uncorrected and predispose to mitochondrial dysfunction with resultant cellular damage.(235-237) This can manifest as organ dysfunction with bacterial translocation and multiple organ failure.(235-237) Numerous studies have demonstrated that increased cardiac output corresponds with improved survival in the setting of major surgery but studies comparing clinician judgement of haemodynamic status and invasive monitoring have shown that clinical assessment is only accurate in approximately 50% of cases.(225, 238-240)
GDFT involves more sensitive monitoring of the systemic circulation by providing indices of perfusion such as cardiac output and aortic blood flow. This results in the administration of patient-specific, situation-specific amounts of intravenous fluid. Mythen et al. have showed that such dynamic optimisation of the systemic circulation has beneficial effects on the gastrointestinal microcirculation with decreased levels of splanchnic acidosis. Some trials have administered a greater quantity of intravenous fluid compared to patients in the control group suggesting the adequate treatment of occult hypovolaemia.

Some trials have shown increased colloid administration in patients receiving GDFT with no difference in the overall amount of intravenous fluid administered. This is partially a consequence of trial protocols which require boluses of colloid to be preferentially given rather than crystalloids. However, the clinical benefits may be a result of the colloids optimising the splanchnic circulation as studies in murine models have shown that colloids are superior to crystalloids in optimising the gastrointestinal microcirculation. Other trials have shown comparable amounts of fluid administration in both treatment and control arms and have proposed that early correction of a functional intravascular fluid deficit attenuates the post-surgical inflammatory response and thus may prevent cellular hypoxia and its adverse consequences. This theory is also supported by decreased postoperative serum levels of the pro-inflammatory cytokine IL-6 in patients receiving GDFT. It is also important to note that even in studies showing no difference in the mean or median volume of fluids administered, the amounts for individual patients are varied and it is precisely the avoidance of pre-defined quantities for fluid administration that may provide clinical benefit.
Intraoperative markers of fluid status have traditionally included monitoring of heart rate, blood pressure and urine output. As mentioned above, heart rate and blood pressure may not be sensitive enough to detect changes in cardiac output and tissue perfusion due to physiological compensation. As a result, GDFT is based upon measurement of other dynamic markers of fluid responsiveness along with supporting evidence from the traditional markers mentioned above.

1.9.3 Tools for GDFT

The measurement of cardiac parameters using invasive techniques was initially accomplished using the pulmonary artery catheter (PAC).(248) This can provide measurements of left atrial pressure as well as left ventricular end diastolic pressure to guide fluid responsiveness. Thermodilution curves can also be acquired using either boluses of fluid or via newer catheters with heated coils. These can provide measurements of preload and afterload and thus allow administration of fluid to maximise oxygen delivery. Modified PACs can also be lodged into the ventricle wall to provide dynamic measurements of mixed venous oxygen saturation to guide fluid therapy. In this context, mixed venous oxygen saturations must be differentiated from central venous oxygen saturations as the latter has been shown to be higher by approximately 5%.(249) Nonetheless, both variables respond similarly to fluid challenges.

Oxygen saturations can be misleading in normovolaemic haemodilution where cardiac output increases with no change in oxygen saturations until the haemoglobin level is sufficiently reduced. Mixed venous and central venous oxygen saturations are also influenced by anaesthesia and postural changes.(250) These have been used to guide early aggressive fluid therapy in sepsis but their use has not been conclusively shown to be of benefit in the intraoperative setting.(251) Moreover, PAC
placement is invasive and is associated with significant morbidity. As a result, previous studies have been conflicting with some indicating either no benefit or even increased harm from perioperative PAC guided management. This has been accompanied by the recognition of other valid markers of fluid responsiveness with minimally invasive methods of assessment.

Measurements of cardiac output and stroke volume can also be obtained via analysis of the pressure waveform derived from arterial lines. The Vigileo™ Monitor and FloTrac™ system (Edwards Lifesciences, Irvine, USA) measure cardiac output in this way. These systems measure pulse rate to include cardiac contractions contributing to tissue perfusion. Instead of directly measuring stroke volume, pressure waveform analysis allows calculation of the variation in arterial pressure. Thus, these instruments are dependent on the basis of stroke volume being proportional to aortic pulse pressure. The measured data are then adjusted using a conversion factor incorporating the effects of vascular tone, age, gender and body-surface area. The monitor thus displays stroke volume, cardiac output, stroke volume variation and other parameters.

Stroke volume variation usually occurs with respiration as arterial pressure decreases during inspiration and increases during expiration as a result of changes in intrathoracic pressure. However, in mechanical ventilation, these changes are reversed and arterial pressure rises on inspiration. The normal variation in these circumstances is approximately 10–15%. An increased amount of stroke volume variation indicates a relative decrease in preload and suggests that the patient may be fluid responsive. Stroke volume variation numerically represents the gradient of the Starling curve and thus increased stroke volume variation is akin to being placed on the steep portion of the Starling curve. Stroke volume variation has been
demonstrated to have both high sensitivity and specificity as a marker of fluid responsiveness in surgical settings and has the advantage of being able to predict fluid responsiveness prior to administration of bolus intravenous fluid, thereby further minimising the risk of inappropriate fluid administration. (254-258)

Similar cardiac parameters can also be obtained using the combination of a thermistor-tipped arterial line and a central venous line using the Pulse Contour Cardiac Output method (PiCCO™) (Pulsion Medical systems, Munich, Germany). This method does not require the insertion of a pulmonary artery catheter and relies on either thermodilution or arterial waveform analysis. Depending on the technique used, it can provide measurements of cardiac output, end-diastolic volume, stroke volume variation and systemic vascular resistance. Thermodilution requires the administration of a saline bolus with measurements of the downstream temperature change. A thermodilution curve is then plotted using the modified Stewart-Hamilton algorithm allowing for calculation of the parameters mentioned above. An important advantage of this technique is that it is not influenced by the ventilatory status of the patient. Arterial waveform analysis also allows measurement of stroke volume, cardiac output and systemic vascular resistance. An important difference between PiCCO™ and the Vigileo™– Flotrac™ system is that the former requires manual calibration as cardiac output is correlated to the area under the pressure waveform, whilst the latter calculates cardiac output based on variability in aortic pulse pressure. PiCCO™ cannot be used in patients with cardiac arrhythmias and importantly, has been described by some authors as being as invasive as pulmonary artery catheters. (259)

Waveform analysis is also possible using the Lithium Dilution Coefficient (LiDCO™) (LiDCO, London, England) technique. This requires an arterial line and a
central or peripheral venous line and initial calibration using values of cardiac output from either another monitor or from a small bolus dose of lithium indicator. This is injected through the venous line and the resulting arterial lithium concentration-time curve is plotted following detection of lithium concentration in withdrawn arterial blood. The use of Lithium as an indicator was first described in 1993.(260) Measurements from the LiDCO™ have been validated against that of PiCCO™ and the thermodilution technique.(261, 262) The doses of Lithium used are not known to cause any adverse effects.(263) The underlying principle is that the intrathoracic blood volume and cardiac output are related to the mean transit time of the lithium indicator. This device also provides dynamic measurements of cardiac output and venous oxygen saturations.

The most widely studied tool in the context of perioperative GDFT is the Oesophageal Doppler Monitor (ODM) (Deltex Medical, Chichester, UK).(264) The ODM measures the velocity of blood in the descending thoracic aorta and provides a graphical representation of this against time. It calculates the area under this curve to measure stroke distance – the distance a column of blood travels during systole. The width of this waveform represents the systolic ejection time and this is corrected using Bazett’s equation to be expressed as corrected flow time (FTc). FTc is inversely proportional to systemic vascular resistance and thus a narrow FTc is an indicator of vasoconstriction. Changes in FTc have been shown to be a sensitive indicator of preload.(265, 266) This information is converted using a pre-programmed normogram incorporating weight, height and age to determine stroke volume.(267) Cardiac output is then determined via multiplication of stroke volume by heart rate. Measurements derived from the ODM have been validated against the pulmonary artery catheter in a variety of settings.(268, 269) The applicability of these measurements to fluid administration are to do with the Frank-Starling law which
states that cardiac contraction is dependent on the degree of stretch imposed by cardiac filling. Therefore left ventricular contraction and stroke volume are dependent on left ventricular end-diastolic volume. In this way left ventricular stroke volume and aortic blood flow can be maximised by increasing cardiac filling using boluses of intravenous fluid. Any improvement in stroke volume is then treated with additional boluses of intravenous fluid until the plateau of the Starling curve is reached as shown in Figure 2.

Fluid responsiveness may also be predicted using a newly designed oxygen saturation probe (Massimo Rainbow™ (Massimo Inc, Irv, CA)). The plethysmographic waveform can be visualised using oxygen saturation probes. There are inherent respiratory variations in this waveform which are a marker of fluid status and preload. The physiological basis of this observation is that mechanical ventilation causes changes in intrathoracic pressure which influence venous return and preload. These changes in preload, as induced by ventilation, influence cardiac function to a greater extent if the patient is fluid responsive as this is akin to being on the steep portion of the Starling curve (See Figure 2). Thus, patients who are fluid responsive show greater respiratory variation in the plethysmographic waveform analogous to pulse pressure variation.

Previous studies have shown that the amplitude of respiratory variations in the plethysmographic waveform (ΔPOP) are a sensitive indicator of preload and fluid responsiveness and correlate well with pulse pressure variation and static indicators of fluid responsiveness.(270) These studies have been conducted intraoperatively and postoperatively as well as in septic patients.(271-273) However, measurement of (ΔPOP) requires specialised equipment and is not feasible in routine clinical practice.
The advent of the Massimo Rainbow™ saturation probe has sought to numerically quantify ΔPOP by developing the Pleth Variability Index™ (PVI). PVI is based upon the changes in the perfusion index over one or more respiratory cycles.(274) The perfusion index is calculated as a percentage figure of the pulsatile and non-pulsatile infrared signals detected by the saturation probe and thus makes an assessment of intravascular volume based on pulsoximeter waveform. PVI has been shown to correlate well with ΔPOP and a PVI value of greater than 14% has been proposed as an indicator of patients who are fluid responsive.(275, 276) PVI measurements have also been shown to correlate well with the Flotrac-Vigileo™ system.(277)

Intraoperative fluid administration based on PVI measurements has been examined in one randomised trial of patients undergoing major abdominal surgery (see below) and was shown to provide clinical benefits.(278) It is important to note that PVI values have not been correlated with measurements from the ODM and have not been validated in patients receiving vasopressors or regional anaesthesia, which may affect vasomotor tone.(274) A meta-analysis of the predictive value of PVI has also shown only moderate accuracy though the analysis was limited by study heterogeneity.(279) PVI values also depend on the constancy of the ventilatory cycle in mechanical ventilation. However, PVI values have the potential to gauge fluid responsiveness in a completely non-invasive manner.

1.9.4 GDFT in major abdominal surgery – Randomised trials

The concept of haemodynamic optimisation was initially shown to be of benefit in sepsis and in conjunction with the work of Shoemaker and colleagues, has been explored in various surgical settings including cardiac surgery, vascular surgery, orthopaedic surgery and abdominal surgery as well as in patients with polytrauma.
The ODM is supported by the largest body of evidence for intraoperative GDFT and has been investigated in a number of randomised trials. The following is a narrative overview of published randomised trials in this field.

**1.9.4.1 Non-ODM trials**

Trials that imposed supranormal values to be obtained (Shoemaker 1988, Lobo 2000,) were excluded as they are not strictly in keeping with the concept of GDFT which emphasises individualised, achievable targets for optimisation.(228, 280) The trial by Boyd et al. has also not been discussed as the intervention in this trial was dopexamine administration rather than intravenous fluids.(281)

Wilson et al. conducted a three-armed study of 138 surgical patients who were randomised to either conventional care or goal-directed care with increased invasive monitoring with supplementary intravenous fluids and inotropes.(282) The two treatment groups differed in the choice of inotrope administered (dopexamine or adrenaline). The treatment groups also received a litre of Hartmann’s solution and boluses of human albumin colloid to achieve pre-determined pulmonary artery occlusion pressures. They demonstrated decreased mortality in the two treatment groups compared to the control arm and showed that patients receiving preoperative dopexamine developed fewer complications compared to patients in the other two arms and had a decreased hospital length of stay. This was a study of preoperative optimisation with an emphasis on dopexamine use. An important difference between the two groups was that the control group did not have as many pts admitted to monitored environments postoperatively so differences in outcome could be attributed to the level of care rather than the intervention itself. Moreover, the study employed preoperative admission to a high dependency unit, which may not be clinically feasible.
Sandham and colleagues conducted the landmark, multi-centred trial investigating goal-directed therapy as guided by perioperative PACs in high risk surgical patients. (253) This trial enrolled 1994 patients and was powered to detect any difference in in-hospital mortality. Patients in the intervention arm received supplementary boluses of intravenous fluid and vasoactive medication to achieve pre-defined physiological goals incorporating numerous parameters of perfusion and flow. The authors reported no difference in mortality or morbidity between the two groups except a higher incidence of pulmonary embolism in patients with PACs. The authors thus recommended that PAC guided therapy was not necessary particularly in light of the invasive nature of PACs. The lack of benefit in this study led to decreased enthusiasm towards the concept of perioperative haemodynamic optimisation until the advent of safer monitoring tools. This study was conducted four years after the study above and focussed on intraoperative optimisation. The investigators enrolled approximately 50% of all eligible patients but did not allow for cross-over and excluded patients when no intensive care beds were available, thus reducing the generalisability of the study. It is also important to note that only up to 80% of the patients actually achieved the pre-set therapeutic goals.

Pearse et al. published a single-centre, partially-blinded study in 2005 evaluating postoperative goal-directed therapy in a 122 surgical patients being managed in the Intensive Care Unit using the LiDCO monitoring system. (283) All patients underwent major abdominal surgery and there were no significant differences between the patients at baseline. The authors demonstrated that patients in the treatment group received a greater volume of intravenous 4% succinylated gelatine solution (Gelofusine; B Braun Medical Ltd; Sheffield; UK) and greater quantities of Dopexamine. These patients experienced fewer complications — which was the primary endpoint — and a decreased hospital length of stay with no difference in
mortality. This study was important in demonstrating the importance of goal-directed therapy in the postoperative setting with the likely implication being that optimisation of perioperative fluid balance can improve clinical outcomes regardless of when implemented. However, the relative importance of timing is debatable for the reasons outlined when discussing the proposed rationale behind goal-directed therapy.

Lopes et al. published a small single-centre, blinded study investigating intraoperative GDFT in 33 patients undergoing high risk surgery. (242) Supplementary boluses of intravenous colloid solution (6% HES) were administered based on an algorithm to decrease pulse pressure variation. The investigators successfully demonstrated decreased variation in pulse pressure in the treatment group with improvements in other physiological proxies of tissue perfusion such as lactate and arterial blood pressure. Patients in the treatment group received a greater quantity of colloids and total intravenous fluid. These patients had significantly decreased hospital length of stay and experienced fewer complications, with the former being the primary endpoint of interest. This study is valuable as it demonstrated the importance of intraoperative haemodynamic optimisation using pulse pressure variation as a marker of fluid responsiveness.

Donati et al. conducted a multi-centred, blinded study of 135 high-risk surgical patients. (284) The authors investigated both intraoperative and postoperative goal directed therapy using boluses of colloid fluids and dobutamine infusions. Alongside conventional monitoring, patients randomised to the treatment group were given supplementary boluses of fluids and pressors as per their measured oxygen extraction, which was calculated from arterial and venous oxygen saturation and represents the balance between tissue oxygen delivery and consumption. The
primary endpoint of this study was organ failure and patients in the treatment group were shown to have decreased incidence of organ failure and significantly lower hospital length of stay. The strength of this study is that goal-directed therapy was employed in both the intraoperative and postoperative period with both fluids and inotropes being administered according to a pre-defined protocol.

Harten et al. conducted a randomised trial of intraoperative GDFT in patients undergoing emergency abdominal surgery to determine the effects of haemodynamic optimisation on renal function. This trial recruited 30 patients and patients in the treatment arm were administered supplementary boluses of Voluven™ based on algorithms to decrease pulse pressure variation as measured by the LiDCO™ system. The authors could not demonstrate any difference in renal function or in clinical outcomes such as length of stay or complications despite an increased amount of Voluven™ being administered. They proposed that this may be due to preoperative resuscitation of all patients, heterogeneous perioperative care or a minimal impact of fluid management on renal function in this setting. Despite these limitations, however, this study was the first trial to evaluate GDFT in emergency abdominal surgery and also identified the potential logistical problems in this context.

Mayer et al. conducted a randomised trial of intraoperative goal-directed therapy in 60 high-risk surgical patients. Therapy in the treatment arm consisted of supplementary boluses of intravenous fluids (colloid and crystalloid) and inotropes as guided by arterial pressure waveform analysis measured by the Vigileo™/FloTrac™ system. The authors demonstrated a relative increase in the proportion of colloid to crystalloid usage in patients randomised to the intervention group with no difference in the total amount of fluids administered. Dobutamine use was also greater in the intervention group. Patients in the intervention group were
shown to have a decreased hospital length of stay – the primary endpoint of the trial – and decreased total complications. This is the first trial to evaluate the use of arterial pressure waveform analysis in this setting.

Forget et al. conducted a randomised trial of intraoperative goal-directed therapy in 82 patients undergoing major abdominal surgery.\cite{278} Patients in the treatment group received boluses of Voluven™ as per measurements of pleth variability index. This trial was powered to detect a difference in post-operative lactate levels. The authors demonstrated decreased crystalloid administration in the intervention group with lower lactate levels in these patients. There was no difference in total complications or hospital length of stay. This is the only trial to date that has evaluated goal-directed therapy using the pleth variability index as the criterion for fluid administration.

### 1.9.4.2 ODM-guided fluid therapy – Trials in non-abdominal surgery

Mythen and Webb conducted a randomised trial of ODM-guided intraoperative GDFT in 60 patients undergoing cardiac surgery.\cite{200} They evaluated gastric mucosal perfusion as a proxy of tissue perfusion using gastric tonometry and demonstrated that perioperative plasma volume expansion using ODM-guided supplementary boluses of 6% HES solution decreased gastric intramucosal pH and thus decreased splanchnic hypoperfusion. The patients in the intervention group received a greater quantity of colloid solutions and experienced fewer complications and decreased hospital length of stay. This was the first trial investigating ODM-guided fluid therapy in a surgical setting and demonstrated the potential benefits in short term recovery with optimised fluid management.

Sinclair and colleagues conducted a randomised trial investigating intraoperative GDFT in 40 patients undergoing repair of proximal femoral fractures.\cite{241} Patients...
in the intervention group were given boluses of HES colloid solution according to ODM measurements. The authors demonstrated optimised cardiac indices in patients treated according to ODM measurements and these patients received greater amounts of fluid overall compared to patients being managed conventionally. Patients in the intervention group had a significantly lower hospital length of stay. This study was extremely important as it was published in a highly regarded, generalist journal, which led to the exposure of GDFT to the wider medical community and policy-makers. Moreover, it also demonstrated a decreased length of stay with ODM use and commented on the possible financial implications of this finding.

Venn and colleagues subsequently published a randomised trial reporting on GDFT in 90 patients undergoing repair for hip fractures.(286) This was a three-armed study with patients being managed either conventionally, as per central venous pressure recordings or as per ODM measurements. Patients randomised to ODM-guided fluid therapy received supplementary boluses of 4% succinylated Gelatin solution to optimise their aortic blood flow and stroke volume. The authors demonstrated that patients receiving ODM-guided fluid therapy received more intravenous fluid overall compared to patients managed conventionally. These patients also experienced less episodes of intraoperative hypotension but no differences in morbidity were noted. Patients in the two intervention groups also satisfied discharge criteria earlier but there was no difference in total hospital length of stay.

McKendry and colleagues conducted a randomised trial of postoperative ODM-guided fluid therapy in 174 patients undergoing cardiac surgery.(287) Patients were randomised to either conventional management or ODM-guided administration of
colloid solution or vasopressors. Patients in the intervention group received greater quantities of colloid solution and were shown to have superior cardiac indices. These patients experienced fewer complications (not statistically significant) and significantly decreased hospital length of stay. The significance of this study was that it focussed on postoperative fluid management alone and was almost entirely nurse-driven. As a result, it was thought to be clinically feasible to conduct GDFT in the post-operative setting for selected patients.

1.9.4.3 ODM-guided fluid therapy – Trials in abdominal surgery

Gan et al. conducted a randomised trial in 100 patients undergoing major abdominal surgery.(288) Patients were randomised to either ODM-guided fluid therapy or conventional fluid management. Patients receiving ODM-guided fluid therapy received 200mL boluses of 6% HES to optimise aortic blood flow and stroke volume. The authors demonstrated optimised cardiac indices in patients managed with the ODM and these patients had earlier recovery of bowel function, shorter hospital length of stay and received greater quantities of colloid fluids. Patients receiving ODM-guided fluid therapy also experienced less nausea and vomiting with no other differences in complications. The authors hypothesised that increased administration of colloid fluids optimised splanchnic perfusion to prevent microcirculatory dysfunction and this was the first trial investigating ODM-guided fluid therapy in major abdominal surgery.

Conway et al. conducted a randomised trial of ODM-guided intraoperative fluid therapy in 57 patients undergoing major colorectal surgery.(243) Patients treated as per ODM protocols received weight-based boluses of HES solution and were shown to receive more colloid fluids compared to patients in the control group. ODM-guided fluid therapy optimised the cardiac indices of patients in the treatment arm but there
were no differences between groups with regards to resumption of bowel function, total complications or hospital length of stay. The authors suggested the lack of differences in clinical outcomes may have been a consequence of a small sample size as trends favoured ODM-guided fluid management. This was the first trial to investigate GDFT specifically in colorectal surgery.

Wakeling et al. subsequently conducted a randomised trial in 128 patients undergoing major colorectal surgery. (244) Patients were randomised to receiving either ODM-guided or conventional fluid management and 250mL boluses of colloid solution were given as per ODM measurements in the intervention group. Patients in the intervention group received a greater volume of intravenous colloid solution with superior cardiac indices as compared to patients in the control group. There was no difference in systemic inflammatory markers but patients treated as per ODM-guided measurements had earlier return of bowel function, superior functional recovery, decreased complications and shorter hospital length of stay.

Noblett et al. conducted a randomised trial of ODM-guided fluid management in 108 patients undergoing major colorectal surgery. (247) Weight-based boluses of 6% HES solution were administered to optimise ODM-derived cardiac indices. The authors showed no significant difference in the amount of fluids administered but showed decreased systemic inflammation as measured by serum IL-6, fewer complications and shorter hospital length of stay in patients treated as per ODM measurements. This was the first trial where allocation concealment and blinding extended to the anaesthetist. Since there was no difference in the amount of intravenous fluids administered, the authors theorised that early correction of occult hypovolaemia may have minimised tissue hypoperfusion, minimised microcirculatory dysfunction and improved clinical outcomes as a result.
Senagore et al. conducted a three-armed study investigating ODM-guided fluid therapy in 64 patients undergoing laparoscopic colectomy within an ERAS program.(289) This is the only study to evaluate GDFT within an ERAS program and compare crystalloid and colloid boluses. This study also used balanced crystalloids Patients were randomised to either conventional management (Group1) or ODM-guided fluid therapy, where boluses of either 200mL of ^% HES solution (Group 2) or 300mL Lactated Ringer's solution (Group 3) were given as per ODM measurements. Patients in group 2 and 3 received significantly more fluid. The authors found no benefit from ODM-guided fluid therapy in this context with patients in group 3 experiencing significantly more complications and longer hospital length of stay. The authors thus concluded that goal directed fluid therapy did not offer an advantage within a mature enhanced recovery programme but also that length of stay may not be ideal primary outcome for such a study.

Challand et al. recently conducted a randomised trial investigating ODM-guided fluid therapy in 179 patients undergoing major colorectal surgery within an ERAS protocol.(290) Patients in the control group were not fluid restricted but instead received ‘standard’ fluid management. The primary outcome of the study was number of days to satisfy pre-defined discharge criteria. Patients randomised to ODM-guided fluid management received a greater quantity of colloid solution and had superior intraoperative cardiac indices. There were no differences in outcome between the two groups with a trend towards more complications and longer length of stay in patients randomised to GDFT. The authors thus concluded that GDFT conferred no additional benefit within their otherwise optimised perioperative environment.
1.9.5 Guidelines and Meta-analyses of GDFT

Initial systematic reviews and meta-analyses showed no convincing clinical benefit from haemodynamic optimisation.(291) A meta-analysis by Kern and Shoemaker, however, suggested that haemodynamic optimisation decreased mortality when instituted early in high risk patients and when administered treatment increased oxygen delivery.(292) A subsequent meta-analysis by Poeze et al. showed that observed impressive results were not found in poorer quality trials alone.(293) The authors also showed that perioperative haemodynamic optimisation of high-risk surgical patients showed the most impressive results in decreasing mortality.

Abbas and Hill conducted a meta-analysis of ODM use in major abdominal surgery.(294) They showed that patients in the intervention group received greater amounts of colloid fluids and had higher cardiac output. Patients receiving ODM-guided treatment had decreased length of hospital stay, decreased complications, decreased ICU admissions, decreased requirement for inotropes and earlier resumption of bowel function with no difference in mortality as a likely consequence of small patient numbers. These findings were subsequently confirmed in two further meta-analyses.(72, 295) Phan et al. conducted a meta-analysis of all trials exploring ODM-guided fluid therapy including all the trials mentioned above and another trial in trauma patients.(296) This study also reported similar findings such as decreased hospital length of stay and decreased complications. Giglio et al. conducted a meta-analysis of all trials evaluating GDFT in abdominal surgery and demonstrated that GDFT reduced both major and minor gastrointestinal complications.(297)

These findings have had significant implications on health policy and clinical care. In the United Kingdom, the Health Technology Assessment committee, on behalf of
the National Institute for Health Research, conducted a review on the utility of the ODM. This review concluded that ODM-guided fluid management provided clinical benefits and was cost-effective. (298) This was also reiterated by the Centre for Evidence-Based Purchasing and as such, the concept of ODM-guided fluid management has been nationally funded and is being gradually introduced into most hospitals. (299, 300) In the United States of America, the Centers for Medicare and Medicaid Services compensate clinicians for use of the ODM as they have deemed it both “reasonable and necessary” for patients requiring intraoperative fluid optimisation. (301, 302) Recently published guidelines concerning optimal perioperative fluid therapy in adult surgical patients and optimal perioperative care in colorectal surgery have also recommended the use of ODM for intraoperative fluid management. (21, 303) Therefore, GDFT and ODM-guided fluid management in particular is a topical issue of scientific and clinical importance.

1.10 Summary

Perioperative fluid management in colorectal surgery significantly influences clinical outcomes. Previous studies have explored different fluid regimens in this setting and the evidence has led to clinical guidelines and health policy decisions which directly affect patient care. However, paradigm shifts in fluid therapy must be viewed alongside the other advancements in perioperative care and there are important questions in this regard that remain unanswered. These questions include exploring the heterogeneity of the perioperative environment within which fluid administration is conducted; determining the feasibility of fluid restriction; exploring attitudes towards clinical use and further study of GDFT; critically appraising the relevant evidence pertaining to GDFT and a comparison of GDFT with other fluid strategies such as fluid restriction in an otherwise homogeneous and optimised
setting. These questions have been further clarified and addressed and form the foundation of this thesis.
2. Perioperative care in colorectal surgery – A survey of anaesthetists from UK, Australia and New Zealand

2.1 Introduction

In chapter one, it was argued that fluid therapy is a vitally important part of the wider field of perioperative care. As such, any investigation of fluid therapy must first define the perioperative context within which it is to be studied since this has an important bearing on fluid administration. There have been numerous advances made in the field of perioperative care as discussed in chapter one. However, clinical implementation of optimised perioperative care is difficult and perioperative practice has been slow to change from historic dogma due to numerous barriers.(304, 305)

Previous surveys of surgeons around the world have aimed to characterise practice regarding perioperative care in colorectal surgery.(24, 306-308) These surveys have shown variable uptake of the individual components of ERAS protocols. However, there are comparatively scarce data regarding anaesthetic practice.(309) This is important since previous work has identified lack of collegial support as an important barrier to the implementation of ERAS protocols.(307) Moreover, it is particularly relevant to this thesis since perioperative fluid management is the dual responsibility of surgeons and anaesthetists.

Thus, a survey of anaesthetists from the United Kingdom (UK) and Australia and New Zealand (AUS/NZ) was conducted to characterise current practice with regards to perioperative care in colorectal surgery. Specific questions were also asked regarding fluid restriction and other aspects of perioperative care which may influence fluid therapy. This would then allow greater understanding of the perioperative context within which fluid administration is conducted.
2.2 Methods

2.2.1 Study design

This study was a cross-sectional survey of randomly selected, consenting anaesthetists from the United Kingdom, Australia and New Zealand.

2.2.2 Survey creation

An electronic survey was created using a commercially available Internet-based service. Questions were based upon matters of clinical interest and were guided by previous surveys in this area. Discrete choices and free text fields were provided. An ordinal Likert scale was also used for applicable questions. The questions are listed in Table 3.

2.2.3 Study set-up

This survey was designed in consultation with the Australia and New Zealand College of Anaesthetists (ANZCA) Trials group. Following approval of content by this organisation, ethical approval was sought and obtained. The final version of the survey was then forwarded to the research coordinator of the Association of Anaesthetists of Great Britain and Ireland (AAGBI). Permission was sought from this organisation as well as ANZCA to administer this survey to their members.

2.2.4 Conduct of study

The survey was then administered electronically to 2000 randomly chosen members of the AAGBI and to 500 randomly chosen members of the ANZCA. Both organisations stipulated this as the maximum acceptable sample size for the survey. Individuals were invited to participate via an email with a covering letter explicitly stating the aim of the study. A hyperlink was provided to access the survey online. The individuals were randomly chosen by the respective organisations and the study investigator had no influence on the sample characteristics. An attempt was made to
distribute the survey to individuals who had not been surveyed recently to minimise survey ‘fatigue’. All respondents remained anonymous to the study investigator. One reminder was sent to all non-responders four weeks after the first invitation. The data collection phase of the survey was declared as closed after a further two weeks, thereby providing a total of six weeks for respondents to participate. The results were subsequently collated and subjected to analysis.

### 2.2.5 Statistical analysis

A two-tailed Fisher’s exact test was used to assess categorical outcomes. A p value of less than 0.05 was defined as statistically significant a priori.

**Table 3:** Survey questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which country do you work in?</td>
<td>UK/Australia or New Zealand</td>
</tr>
<tr>
<td>What is your place of practice?</td>
<td>Tertiary Hospital/District (Community) Hospital/Private practice</td>
</tr>
<tr>
<td>What is your current position?</td>
<td>Trainee/Consultant &lt; 5 years/Consultant 5–10 years/Consultant &gt; 10 years</td>
</tr>
<tr>
<td>Are you involved in ANY colorectal surgical anaesthesia?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Do you have an ERAS protocol at your institution?</td>
<td>Yes/No/Unsure</td>
</tr>
<tr>
<td>Are the operations predominantly?</td>
<td>Open/Laparoscopic/HALS/Combination</td>
</tr>
<tr>
<td>Is oral bowel preparation used?</td>
<td>Always/Sometimes (Left sided cases)/Sometimes- as per surgeon/Never</td>
</tr>
<tr>
<td>How many hours preoperatively are clear fluids allowed? (e.g. 8)</td>
<td></td>
</tr>
<tr>
<td>How many hours preoperatively are solids allowed?</td>
<td></td>
</tr>
<tr>
<td>Do you use preoperative oral carbohydrate loading?</td>
<td>Always/Sometimes/Never</td>
</tr>
<tr>
<td>Do you employ fluid restriction?</td>
<td>Intraoperatively/Postoperatively/No</td>
</tr>
<tr>
<td>Do you use regional, opioid-sparing anaesthesia techniques (e.g. epidural)?</td>
<td>Yes (unless contraindicated)/Selectively/Never</td>
</tr>
<tr>
<td>Which techniques do you favour? (Choose as many as applicable)</td>
<td>Epidural/Intrathecal morphine/Transversus Abdominis Plane blocks/Intraperitoneal local anaesthetic/Other (Please specify)</td>
</tr>
<tr>
<td>Do you use epidurals? (Tick as many as applicable)</td>
<td>Preoperatively/Intraoperatively/Postoperatively</td>
</tr>
<tr>
<td>Which postoperative day do you remove epidurals? (e.g. 2)</td>
<td></td>
</tr>
<tr>
<td>What drugs do you use in your epidurals?</td>
<td>Local anaesthetic/Opioid/Combination</td>
</tr>
</tbody>
</table>
2.3 Results

2.3.1 Response rate and demographics

Responses were received from 709 anaesthetists from the UK and 169 anaesthetists from and AUS/NZ. The response rates from the UK and AUS/NZ were 35% and 34% respectively. Within these respondents, there were 599 anaesthetists who were involved in colorectal surgery (UK: 464; AUS/NZ: 135). The survey completion rates in the UK and AUS/NZ were 91% and 89% respectively. The demographic characteristics of the respondents are as per Table 4. The UK sample was less experienced overall due to the inclusion of trainees (p<0.01).

Table 4: Demographic characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UK</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Place of practice</td>
<td></td>
</tr>
<tr>
<td>Tertiary hospital</td>
<td>211</td>
</tr>
<tr>
<td>District/Community hospital</td>
<td>276</td>
</tr>
<tr>
<td>Private practice</td>
<td>55</td>
</tr>
<tr>
<td>Experience</td>
<td></td>
</tr>
<tr>
<td>Trainee</td>
<td>128</td>
</tr>
<tr>
<td>Consultant &lt; 5 years</td>
<td>99</td>
</tr>
<tr>
<td>Consultant 6–10 years</td>
<td>67</td>
</tr>
<tr>
<td>Consultant &gt; 10 years</td>
<td>163</td>
</tr>
</tbody>
</table>

2.3.2 Perioperative practices

The data regarding the presence of an ERAS protocol in each region are shown in Figure 3. The respondents from the UK were significantly more likely to have an ERAS protocol in place (p<0.01) compared to respondents in AUS/NZ. The data regarding individual elements of perioperative care are as per
Table 5. The use of routine bowel preparation was more common in AUS/NZ as compared to the UK ($p < 0.01$). Preoperative carbohydrate loading was infrequently used overall but was most commonly used in the UK compared to AUS/NZ ($p<0.01$). The majority of respondents in AUS/NZ never used preoperative carbohydrate loading. A considerable proportion of respondents never utilised fluid restriction perioperatively.

**Figure 3:** Does your institution have an ERAS protocol in place?
Table 5: Perioperative care

<table>
<thead>
<tr>
<th>Perioperative care</th>
<th>Regions</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>UK</td>
<td>AUS/NZ</td>
</tr>
<tr>
<td>Operation Type</td>
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<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Open</td>
<td>95</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Lap</td>
<td>76</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>HALS</td>
<td>18</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Combination</td>
<td>249</td>
<td>57</td>
<td>65</td>
</tr>
<tr>
<td>Use of Bowel prep</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>73</td>
<td>17</td>
<td>43</td>
</tr>
<tr>
<td>Sometimes – Left sided cases</td>
<td>43</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sometimes – as per surgeon</td>
<td>279</td>
<td>66</td>
<td>55</td>
</tr>
<tr>
<td>Never</td>
<td>28</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Preoperative starvation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solids (Median (Range))</td>
<td>6</td>
<td>2–48</td>
<td>6</td>
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<tr>
<td>Liquids (Median (Range))</td>
<td>2</td>
<td>2–12</td>
<td>3</td>
</tr>
<tr>
<td>Preoperative carbohydrate loading</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>88</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Sometimes</td>
<td>150</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>Never</td>
<td>185</td>
<td>44</td>
<td>93</td>
</tr>
<tr>
<td>Intravenous fluid restriction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperatively</td>
<td>118</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Postoperatively</td>
<td>104</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Never</td>
<td>255</td>
<td>53</td>
<td>71</td>
</tr>
<tr>
<td>Prokinetics</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>9</td>
<td>2</td>
<td>8</td>
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<tr>
<td>Sometimes</td>
<td>163</td>
<td>37</td>
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</tr>
<tr>
<td>Never</td>
<td>264</td>
<td>61</td>
<td>89</td>
</tr>
<tr>
<td>Sedatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>20</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Sometimes</td>
<td>156</td>
<td>36</td>
<td>51</td>
</tr>
<tr>
<td>Never</td>
<td>254</td>
<td>59</td>
<td>51</td>
</tr>
</tbody>
</table>

Lap: Laparoscopic; HALS: Hand-assisted laparoscopy

2.3.3 Anaesthesia

Preferences regarding regional anaesthesia are shown in Table 6 <0.01). Respondents from all regions favoured using regional anaesthetic techniques and epidural anaesthesia specifically was most commonly routinely utilised in the UK (p<0.01). Further details regarding the use of epidural analgesia are shown in Table 7. There was interest in transverse abdominis plane (TAP) blocks in both the UK (27%) and AUS/NZ (28%).
Table 6: Regional anaesthesia

<table>
<thead>
<tr>
<th>Perioperative care</th>
<th>Regions</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UK</td>
<td>AUS/NZ</td>
<td></td>
</tr>
<tr>
<td>Regional anaesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>267</td>
<td>62</td>
<td>40</td>
</tr>
<tr>
<td>Sometimes</td>
<td>161</td>
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<td>Never</td>
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<td>1</td>
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<tr>
<td>Epidural</td>
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<td>60</td>
<td>88</td>
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<tr>
<td>Intrathecal</td>
<td>60</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>TAP block</td>
<td>177</td>
<td>27</td>
<td>48</td>
</tr>
<tr>
<td>IPLA</td>
<td>19</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

IV: Intravenous; TAP: Transversus Abdominis Plane; IPLA: Intraperitoneal Local Anaesthetic

Table 7: Epidural analgesia

<table>
<thead>
<tr>
<th>Epidural analgesia</th>
<th>Regions</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UK</td>
<td>AUS/NZ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Timing</td>
<td></td>
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<tr>
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<td>111</td>
<td>12</td>
<td>26</td>
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<tr>
<td>Intraoperatively</td>
<td>429</td>
<td>45</td>
<td>93</td>
</tr>
<tr>
<td>Postoperatively</td>
<td>408</td>
<td>43</td>
<td>92</td>
</tr>
<tr>
<td>Median day of removal (Range)</td>
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<td>1–5</td>
<td>3</td>
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<tr>
<td>Drug content</td>
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<tr>
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<td>1</td>
<td>3</td>
</tr>
<tr>
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<td>154</td>
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</tbody>
</table>

LA: Local anaesthetic

2.4 Discussion

This survey of 599 anaesthetists from the UK and AUS/NZ has shown significant variation in the perioperative care of patients undergoing colorectal surgery. The routine use of bowel preparation was more common in AUS/NZ and respondents indicated that this was according to the surgeon’s preferences. Preoperative carbohydrate loading was infrequently used overall. A considerable proportion of respondents never utilised fluid restriction perioperatively. Regional anaesthesia in
the form of epidural analgesia was favoured by most anaesthetists. These elements of care have an important bearing on perioperative fluid administration.

The individual aspects of perioperative care investigated here and their relationships to each other deserve further discussion. This survey indicates that many patients still receive bowel preparation either routinely or as per the surgeon’s discretion. This practice is not supported by current evidence apart from perhaps in rectal surgery.(28) Moreover, this influences perioperative fluid management since compensatory fluid administration is recommended when bowel preparation is used to avoid a preoperative functional intravascular deficit.(311) Bowel preparation also prolongs preoperative fasting which is detrimental and further exacerbates preoperative dehydration. The data showed that fasting times are largely in keeping with recommendations but also that there is a wide range of times. Some respondents justified these as being a consequence of bowel preparation. Studies of fluid therapy should hence account for the potentially greater fluid requirement of patients receiving bowel preparation.

Similarly, preoperative carbohydrate loading was infrequently used. Preoperative carbohydrate loading has been shown to attenuate postoperative catabolism, reduce preoperative discomfort and may be associated with decreased complications.(29) Furthermore, carbohydrate loading also protects against preoperative dehydration. Since previous work has suggested that early correction of a prevalent fluid deficit may decrease post-surgical inflammation and improve postoperative outcomes, the maintenance of preoperative normovolaemia is crucially important.(247) The avoidance of fasting and preoperative carbohydrate loading is therefore likely to influence intravenous fluid administration.
It is important to note that the individual elements of the perioperative care protocol are linked and thus variable implementation of one aspect influences whether the other elements can be administered. This is also logistically important to acknowledge since interdependent elements may be dependent on different personnel (Surgeon: Bowel Preparation, Nurse: Preoperative Carbohydrate drink; Anaesthetist: Intraoperative intravenous fluids).

The responses with regards to perioperative fluid management encapsulate the contentious nature of this field in the context of colorectal surgery. As discussed in the introduction, current evidence suggests potential benefit from both restrictive and goal-directed fluid regimens. However, there are important questions that remain unanswered with both fluid regimens. Although fluid restriction may in fact just represent the avoidance of fluid overload and maintaining patients in a state of fluid balance, previous studies have demonstrated that restrictive regimens may lead to forced hypovolaemia and cause harm. Since perioperative fluid administration is the dual responsibility of surgeons and anaesthetists, further collaboration and study is required to determine the ideal regimen and determine congruent practice in both the intraoperative and postoperative phase.

A limitation of this study was that it was not possible to select a sample of colorectal-specific anaesthetists in the same way that subspecialist surgeons have been sampled in previous surveys. Moreover, these findings need to be considered alongside the caveat of a moderate response rate which may have led to the self-selection of individuals with a strong opinion – positive or negative – in these matters. It should also be acknowledged that respondents from the UK included anaesthetic trainees whilst in Australia and New Zealand, the responses were exclusively from consultant anaesthetists. This may cause a generational difference.
in the sampling frame, though it is likely that the practice of trainees is largely dictated by their consultants.

Variable adherence to individual elements has the potential to undermine the ability to deliver other aspects of the ERAS protocol. Moreover, an increasingly important question is the role of an individual aspect of perioperative care such as intravenous fluid therapy within an otherwise optimised, homogeneous perioperative care setting. This requires studies to be conducted within an ERAS setting. Despite its limitations, this survey has demonstrated considerable variation in perioperative practice from an anaesthetic perspective. The perioperative environment can influence intravenous fluid administration and any heterogeneity needs to be considered when evaluating or designing studies investigating perioperative fluid therapy.
3. Perioperative fluid therapy in elective colectomy in an Enhanced Recovery program

3.1 Introduction

In chapter two, it was shown that there is considerable heterogeneity in the perioperative care of patients undergoing colorectal resection. Any study of fluid administration is variably influenced by the other elements of perioperative care. In a setting where perioperative care is standardised, however, fluid management is more easily able to be evaluated with greater confidence that observed results are not confounded by other variables.

As discussed in the introduction, there are currently two fluid strategies that are thought of as optimal. One of these is perioperative fluid restriction, which has been favoured by some institutions within an ERAS setting where there is avoidance of bowel preparation and an emphasis on preoperative carbohydrate loading and early oral intake.(21)

Excessive fluid restriction can, however, predispose to hypovolaemia and hypoperfusion leading to organ dysfunction and death.(71) Trials in major abdominal surgery, as well as more recent trials in colorectal surgery, have raised these concerns.(217, 219, 221) Moreover, there are differences between the published trials with regards to when fluid restriction has been implemented (e.g. intraoperatively or perioperatively) with postoperative fluid administration not standardised when the intraoperative period is being investigated.(223) It is not known if intraoperative fluid restriction simply results in extra compensatory fluid being administered postoperatively. This is especially important in people with significant comorbidities who have less physiological reserve and may require more
carefully calibrated fluid administration. It is the clinical feasibility of such a standardised approach that deserves investigation.

Therefore, this study aims to answer whether intraoperative fluid restriction can be implemented uniformly in patients undergoing elective colectomy within an ERAS protocol – regardless of their comorbidities – without the need for compensatory postoperative fluid and to determine any association between administered fluid amounts and clinical outcomes. It also serves the secondary purpose of determining the existing fluid management within our setting for the planning of any comparative studies.

3.2 Methods

In this study, and the study described in chapter seven, perioperative care was standardised according to the principles of ERAS. The individual components of this pathway as employed within the institution are described below.

3.2.1 Institutional details

Manukau Surgical Centre is an elective surgical facility with operating rooms, two surgical wards and a four bed High Dependency Unit. Staff were trained to work within the ERAS protocol, which has been formally in place since 2005. Patients were identified at either the surgical outpatient clinics or at preadmission clinics.

ERAS was the standard of care for all patients undergoing elective open, laparoscopic or hand-assisted laparoscopic colectomy. This consisted of the following procedures:

- Ileocolic resection
- Right hemicolectomy
- Extended Right hemicolectomy
- Transverse colectomy
- Left hemicolectomy
- High Anterior resection
- Sigmoid colectomy
- Subtotal colectomy
- Total colectomy

3.2.2 Exclusion criteria

Patients were excluded from the formal ERAS program if they met any of the following criteria:

- Stoma formation
- ASA score of 4 or 5(313)
- Rectal resection (Defined as less than 15cm from the anal verge)
- Non-english speaking and without english-speaking relative/friend for accompaniment
- Significant cognitive impairment

3.2.3 Preoperative

All patients were assessed regarding their fitness to undergo surgery. This involved a detailed history and physical examination. Any comorbidities identified were investigated as appropriate and optimised if possible. Particular attention was paid to the social history and potential factors delaying discharge were resolved preoperatively such as social support at home upon discharge. Nutritional assessment was carried out and patients were prescribed Fortisip™ (Fortisip, Nutricia Inc, Auckland, New Zealand) if required for preoperative caloric supplementation. Routine Investigations included blood tests and an electrocardiograph (ECG). A formal anaesthetic opinion was sought for each patient.

Operations including potential complications were discussed in detail whilst obtaining informed consent.
A dedicated education session was then carried out to introduce patients to the practice and philosophy of the ERAS pathway. Patients were told about the key events in each part of the perioperative process from admission till post-discharge follow up. This process also ensured patients’ understanding of the key milestones and explicit goal-setting. Some of these included:

- Preoperative cessation of alcohol intake and smoking (if applicable)
- Resuming early postoperative intake
- Continuing caloric supplementation postoperatively whilst in hospital
- Mobilisation from postoperative day zero

3.2.3.1 Discharge criteria

Standardised discharge criteria are as below. These were explained to the patient as well to ensure joint understanding of fitness for discharge.

- Dependence on oral forms of analgesia/antiemetics only with trend towards decreasing use
- Resumption of bowel function (passage of flatus). Passage of bowel motion was not considered necessary pre-discharge
- Tolerance of solid foods with no emphasis on quantity
- Normal nursing observations:
  - Temperature >36 and < 37.5
  - Heart rate < 90
  - Oxygen saturation > 93%
  - Systolic Blood pressure > 100
  - Respiratory rate >10 and < 16
  - Mobilising at least to and from the toilet
  - Adequate social supports at home

The preoperative education session was concluded with a tour of the inpatient ward to familiarise the patient with the staff and surroundings. An empty inpatient room was shown to the patient. Written information was then provided to reinforce the education session.
3.2.4 Patient admission

Patients were only admitted on the morning of surgery unless they required bowel preparation. Upon admission, another preoperative nursing assessment was carried out with the administration of an enema if required (see below) and stoma marking as appropriate. Preoperative carbohydrate drinks were administered (see below). Surgical consent was reaffirmed and anaesthetic consent was obtained.

3.2.5 Preoperative Nutrition

Nutritional assessment was carried out and patients were prescribed Fortisip™ (Fortisip, Nutricia Inc, Auckland, New Zealand) if required for preoperative caloric supplementation.

All patients were given preoperative carbohydrate supplementation. This is in the form of two 200mL carbohydrate drinks (Preop™, Nutricia, Auckland, New Zealand) on the morning of the operation, two hours prior to the expected time of surgery.

3.2.6 Bowel preparation

This was used in selected left-sided cases as per the surgeon’s preference. If required, patients were admitted one day prior to surgery and were given one litre of supplementary intravenous fluid (Plasmalyte™, Bayer Healthcare, Auckland, New Zealand). All other left sided cases received an enema on the morning of surgery (Fleet phosphate, 120mL, 19g of monobasic sodium phosphate and 7g of dibasic sodium phosphate).

3.2.7 Anaesthesia

3.2.7.1 Premedication

- Paracetamol 1–1.5g po
- Intravenous dexamethasone 8mg (DBL Dexamethasone Sodium Phosphate Injection, Hospira NZ Limited, Wellington, New Zealand)
3.2.7.2 General anaesthesia

- Induction agent: Propofol (Propofol injection 20mg/mL, Intermed Medical Ltd, Auckland, New Zealand)
- Maintenance anaesthesia: Desflurane (Suprane™, Desflurane USP, Baxter healthcare Ltd, Auckland, New Zealand)
- Neuromuscular blockade: Rocuronium (Esmeron™, Rocuronium bromide, Pharmaco Ltd, Auckland, New Zealand) or Atracurium (Tracrium™, Atracurium besylate, GlaxoSmithKline Ltd, Auckland, New Zealand)
- Intraoperative opioids: Short-acting agents were used. Remifentanil (Ultiva™, Remifentanil hydrochloride, GlaxoSmithKline Ltd, Auckland, New Zealand) or Fentanyl (Fentanyl citrate, AstraZeneca Ltd, Auckland, New Zealand)
- Intraoperative antiemetics: Ondansetron (Zofran™, Ondansetron hydrochloride dehydrate, GlaxoSmithKline Ltd, Auckland, New Zealand) or Droperidol (Droleptan™, AFT Pharmaceuticals, Auckland, New Zealand)

3.2.7.3 Epidural analgesia

Middle or low thoracic epidural catheters were inserted preoperatively. The level of insertion was dependent on the surgical incision and anaesthetic assessment. Epidural catheters were loaded intraoperatively with a combination of local anaesthetic (0.25% Bupivacaine) and low dose opioid (100/200mcg Fentanyl). Dosage was dependent on haemodynamic parameters and anaesthetist assessment. Epidural analgesia was stopped 48 hours postoperatively and removed as appropriate with timing of enoxaparin administration. Patient controlled analgesia pumps were used in the instance of epidural failure.

3.2.7.4 Intraoperative fluid management

As discussed below.

3.2.7.5 Epidural-related hypotension

This was defined as Systolic blood pressure of less than 100 with no concerns regarding other causes of haemodynamic instability (e.g. bleeding). It was primarily
treated with low dose vasopressors (Aramine™ Metaraminol Bitartrate, Merck Sharp and Dohme, Auckland, New Zealand) as well as fluid boluses. Fluid boluses were avoided as much as practically possible and patients were admitted into the high dependency unit for postoperative vasopressor infusions if required.

3.2.8 Surgery

The World Health Organisation Surgical Safety Checklist was used. (59) Antibiotic prophylaxis was administered and consisted of a Cephalosporin (Cefuroxime sodium or Cefoxitin Sodium, Mefoxin™, Merck Sharpe & Dohme, Auckland, New Zealand) and Metronidazole (Pharmacia Ltd., Auckland, New Zealand). Operations were performed with the following approaches:

- Midline laparotomy
- Transverse incisions for right hemicolecetomy (as per surgeon discretion)
- Laparoscopic
- Hand-assisted laparoscopic
- Bowel anastomosis was achieved using circular or linear stapling devices with a confirmed negative air leak test intraoperatively.

3.2.9 Post-anaesthetic care unit

The efficacy of epidural analgesia was confirmed here and postoperative infusion begun (0.125% Bupivacaine and Fentanyl 2mcg/ml solution) and patients were transferred to the ward thereafter at the earliest possible time.

3.2.10 Nasogastric tubes

These were only used for gastrointestinal ileus and/or repeated episodes of vomiting with risk of aspiration.

3.2.11 Urinary drainage

In-dwelling catheters were removed on the morning of post-operative day one following insertion at the time of the operation. A urine output of more than
0.5mL/hr/kg averaged over four hours in otherwise well patients was considered adequate.

3.2.12 HDU care

Patients with significant comorbidities had planned admission into the HDU for the first 24 hours after surgery. These patients were managed with closer monitoring including telemetry. If arterial lines were placed intraoperatively, these were kept in situ during HDU stay. HDU stay was also utilised for postoperative vasopressor infusions.

3.2.13 Oral intake

Early postoperative oral intake was encouraged as explained to the patients preoperatively. Patients were encouraged to drink from the day of the operation with an aim of 800mLs oral intake on the day of the operation. Fortisip™ protein drinks were also given for the duration of hospital stay in addition to meals and patients were to aim to consume four cartons per day. Patients were expected to consume at least 2000mL of oral fluids per day including the caloric supplements. Solid meals are provided to the patient from the evening of the operation and patients were encouraged to consume as much or as little as they wished.

3.2.14 Postoperative fluid management

As discussed below.

3.2.15 Antiemetics

Anti-emetic medications were administered pre-emptively. The drugs of choice were:

- Ondansetron 4–8mg PO/IV q8h/PRN
- Cyclizine 25–50mg PO/IV q8h/Prn
- Droperidol 0.625mg IV PRN
3.2.16 Analgesia

Epidural analgesia was utilised until 48 hours postoperatively. If epidural catheters could not be placed or provided an unsatisfactory block, then patient controlled analgesia in the form of intravenous morphine pumps were utilised.

3.2.16.1 Oral analgesia

- Regular paracetamol 1g PO QID is prescribed
- Breakthrough pain was controlled with the following medications:
  - Tramadol Hydrochloride, 50-100mg PO QID/PRN (AFT Pharmaceuticals Ltd, Auckland, New Zealand)
  - Morphine sulphate tablet 10–20mg, oral Q2-4h/PRN (Sevredol™, Douglas Pharmaceuticals Ltd, Auckland, New Zealand)
  - Morphine sulphate sustained release capsules 10–20mg, oral, bd (M-eslon™, Douglas Pharmaceuticals Ltd, Auckland, New Zealand)
  - Tenoxicam 20mg, oral, bd (Tilcotil™, Valeant Pharmaceuticals Ltd, Auckland, New Zealand)

3.2.17 Deep vein thrombosis prophylaxis

- All patients were required to wear thrombo-embolic deterrent stockings (TED) during the entire hospital stay
- Intermittent pneumatic calf compression were used intraoperatively
- Low molecular weight heparin was prescribed postoperatively until discharge (Enoxaparin Sodium, Clexane ™, Sanofi-Aventis, Auckland, New Zealand)

3.2.18 Mobilisation plan

The importance of early mobilisation was explained to patients during the preoperative education session. The following goals were thus set:

- Two hours out of bed on the day of the operation
- Mobilisation to shower and bathroom from postoperative day 1
- Eight hours out of bed including two walks around the ward on each postoperative day
3.2.19 Discharge information

Patients were provided written information at time of discharge with information on when and how to seek help. Patients were provided with the ward phone number to contact nursing staff if they had any queries that could be safely answered without a formal consultation. Patients were discharged with at least one week’s supply of oral analgesia.

3.2.20 Post-discharge follow-up

- Patients were called at home on post-discharge day 1
- Patients were seen in the outpatient clinic at 7–10 days postoperatively for review of histology, removal of staples/ sutures and general clinical review
- Patients were seen six weeks postoperatively and thereafter at six monthly or yearly intervals in accordance with oncological progress if applicable

3.3 Methods specific to this study

3.3.1 Study set-up

Regional and institutional ethical approval was obtained for this study.

3.3.2 Study design

This was a retrospective review of prospectively collected data.

3.3.3 Study scope

Data were reviewed for patients who had undergone elective colectomy from September 2006–2010 within the ERAS programme at Counties Manukau District Health Board, Auckland, New Zealand.

3.3.4 Data points of interest

Data recorded included demographic characteristics, American Society for Anesthesiology (ASA)(313) score, operation type, operation duration, amount of perioperative intravenous fluids received, hospital length of stay and complications
as per pre-defined criteria and as graded by the Clavien-Dindo classification. (314-316) Complications of grade three and above were defined as major complications. Perioperative fluid amounts were stratified by ASA, which was used as a proxy of comorbidity status as well as by the presence of complications. Pre-complication fluid amounts were defined as the amount of fluid received until the day prior to the complication being first diagnosed. Blood transfusions were considered as colloid fluids for the purposes of this study.

3.3.5 Relevant definitions

The intraoperative period was defined as when the patient was in the operating theatre. Any time before or after this (including time spent in the post anaesthetic care unit) was designated as the preoperative and postoperative period respectively.

3.3.6 Perioperative fluid management

Patients received one litre of preoperative crystalloid (Plasmalyte™ 148, Baxter Healthcare, NSW, Australia) if they were having a left sided resection and were receiving bowel preparation. Intraoperative IVF was restricted to two litres which could include up to 500mls of colloid solution (Gelofusin, Braun Healthcare, NSW, Australia). A further 500mLs of crystalloid was allowed per hour for every hour beyond three hours. Blood loss was initially replaced with IVF and blood products were used if haemoglobin (Hb) dropped below 100g/L in patients with documented cardiac disease or less than 80g/L in otherwise well patients. Intraoperative vasopressors were used as per the discretion of the anaesthetist and metaraminol was the most common agent. All intravenous fluids were stopped by default by nurses when patients arrived on the ward, typically one to three hours after surgery and oral intake of food, fluids and supplements was encouraged. The patient was then formally assessed by the ward doctor to decide whether any intravenous fluid
was necessary. Clinicians were required to see the patient and document their findings and were not allowed to make decisions over the phone. This judgement was based on patient observations, clinical examination and urine output. Examination findings consistent with volume deficit were required to prescribe intravenous fluid (e.g. decreased jugular venous pulse). Intravenous fluid was administered if patients were oliguric (defined as less than 0.5ml/kg/hr averaged over four hours) or had deranged physiological parameters suggestive of volume deficit (tachycardia (>90bpm), hypotension (systolic blood pressure < 90mmHg in the presence of a functioning epidural; <100mmHg without an epidural) Intravenous fluid was also administered for resuscitative purposes in the event of complications, to compensate for losses or for prolonged poor oral intake such as in paralytic ileus.

3.3.7 Statistical analysis

Statistical significance was determined using the two-tailed Fisher’s exact test for categorical data, and the Mann-Whitney U test for continuous data. Univariate analysis was conducted and a logistic regression model was created to control for known potential confounders with the independent effect of each variable subsequently evaluated. A $p$ value < 0.05 was considered as statistically significant.

3.4 Results

3.4.1 Patient details and overall clinical outcomes

From September 2006 to September 2010 there were 227 patients who underwent elective colectomy within our ERAS program. Patient details are as per Table 8 and have been stratified by the occurrence of complications. Increasing age, male gender, increasing ASA score and the presence of malignancy were associated with increased complications. Further details regarding clinical outcomes are as per Table 9.
**Table 8: Patient details**

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<th>Total</th>
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<td>227</td>
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<td>0.07</td>
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<td>109</td>
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<td>1.00</td>
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<td>45</td>
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<td>1.00</td>
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</tr>
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<td>117 (52)</td>
<td>0.11</td>
<td>125 (58)</td>
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<td>10</td>
<td>0.53</td>
<td>25</td>
</tr>
</tbody>
</table>

Cx: Complications; HALS: Hand-Assisted Laparoscopic Surgery

**Table 9: Clinical outcomes**

<table>
<thead>
<tr>
<th>30 day Complications</th>
<th>107/227</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
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</tr>
<tr>
<td>ASA 1</td>
<td>16/46 (35%)</td>
</tr>
<tr>
<td>ASA 2</td>
<td>50/109 (46%)</td>
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<tr>
<td>ASA 3</td>
<td>41/72 (57%)</td>
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<tr>
<td>Total number</td>
<td>167</td>
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<td>Grade 1</td>
<td>19</td>
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<td>Grade 2</td>
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<td>Grade 3</td>
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<td>Grade 4</td>
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</tr>
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<td>Grade 5</td>
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<tr>
<td>Wound</td>
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<tr>
<td>Urinary</td>
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<td>Ileus</td>
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<td>Anastomotic leak</td>
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<td>Other</td>
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<tr>
<td>Median Length of Stay-days (range)</td>
<td>5 (3–65)</td>
</tr>
</tbody>
</table>
3.4.2 Perioperative fluid management

The amounts of IVF administered both intraoperatively and postoperatively have been stratified by both ASA scores and the occurrence of complications and are as per Table 10. There were no statistically significant differences in administered fluid amounts between patients with different ASA scores. All these non-significant p-values have not been noted to prevent clutter within the table. Statistical analysis pertaining to postoperative crystalloid administration has been shown in Table 10 since the median amounts suggest ASA-based differences if the p-values are not considered (ASA 1: 2000mL, ASA 2: 2240mL, ASA 3: 3190mL).

Table 10: Fluid amounts stratified by ASA and complications

<table>
<thead>
<tr>
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<th>Crystalloid</th>
<th>Colloid</th>
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<tr>
<td></td>
<td>Intraoperative</td>
<td>Postoperative</td>
<td>Intraoperative</td>
</tr>
<tr>
<td>ASA 1 (n=30)</td>
<td>2000 (1000–4000)</td>
<td>2000 (0–7200)</td>
<td>0 (0–1000)</td>
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<tr>
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<td>0 (0–500)</td>
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<tr>
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<td>2000 (0–51827)</td>
<td>0 (0–1000)</td>
</tr>
<tr>
<td>ASA 2 (n=59)</td>
<td>2000 (1000–4000)</td>
<td>2000 (0–1000)</td>
<td>0 (0–1000)</td>
</tr>
<tr>
<td>ASA 2 (n=50)</td>
<td>2000 (1000–5000)</td>
<td>4000 (0–39836)</td>
<td>0 (0–1000)</td>
</tr>
<tr>
<td>ASA 2 (n=109)</td>
<td>2000 (1000–5000)</td>
<td>2240 (0–39836)</td>
<td>0 (0–1750)</td>
</tr>
<tr>
<td>ASA 3 (n=30)</td>
<td>2000 (1000–4000)</td>
<td>2550 (0–8450)</td>
<td>0 (0–1000)</td>
</tr>
<tr>
<td>ASA 3 (n=42)</td>
<td>2000 (1000–4000)</td>
<td>4200 (1000–18230)</td>
<td>0 (0–1000)</td>
</tr>
<tr>
<td>ASA 3 (n=72)</td>
<td>2000 (1000–4000)</td>
<td>3190 (0–18230)</td>
<td>0 (0–1000)</td>
</tr>
<tr>
<td>Cx Total</td>
<td>2000 (1000–5000)</td>
<td>4290 (0–51827)</td>
<td>0 (0–1750)</td>
</tr>
<tr>
<td>ØCx Total</td>
<td>2000 (300–4000)</td>
<td>2000 (0–8450)</td>
<td>0 (0–1000)</td>
</tr>
</tbody>
</table>

ASA: American Society for Anesthesiology; ØCx: Patients without complications; Cx: Patients who developed a complication. All values are median (range)
Patients who experienced complications received significantly greater amounts of crystalloid (4290mL vs. 2000mL; \(p<0.01\)) and total IVF postoperatively (5000mL vs. 2000mL; \(p<0.01\)). Increased IVF amounts were also associated with increased hospital length of stay (\(p<0.01\)). There was a non-significant trend towards higher pre-complication fluid amounts in patients who developed major complications (\(p=0.07\)).

### 3.4.2.1 Logistic regression model

Using a logistic regression model (Table 11), age, gender, ASA and presence of malignancy were not independently associated with the occurrence of complications. Postoperative crystalloid administration remained associated with increased complications (\(p<0.01\)). The overall predictive model of occurrence of complications was significant (Chi-Squared value = 50.6; \(p<0.01\)).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95%CI)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.98–1.04)</td>
<td>0.57</td>
</tr>
<tr>
<td>Female Gender</td>
<td>0.56 (0.31–1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>ASA 1</td>
<td>0.49 (0.18–1.29)</td>
<td>0.15</td>
</tr>
<tr>
<td>ASA 2</td>
<td>0.76 (0.38–1.52)</td>
<td>0.44</td>
</tr>
<tr>
<td>ASA 3</td>
<td>2.06 (0.78–5.48)</td>
<td>0.15</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0.64 (0.30–1.39)</td>
<td>0.26</td>
</tr>
<tr>
<td>Postoperative crystalloid</td>
<td>1.74 (1.41–2.31)</td>
<td>(&lt;0.01)</td>
</tr>
</tbody>
</table>

### 3.5 Discussion

This study has outlined the current practice of fluid therapy within our institution and demonstrated the feasibility of intraoperative fluid restriction. This strategy has been recommended in colorectal surgery as it has been shown to decrease complications. However, to the author’s knowledge, this is the first study to specifically assess the impact of intraoperative fluid restriction on postoperative fluid
administration within an ERAS protocol. This study has shown that intraoperative fluid restriction does not lead to compensatory postoperative IVF being administered in patients with more comorbidities, as defined by ASA scores. Any perceived differences in postoperative crystalloid administration with increasing ASA scores are offset by markedly non-significant statistical differences.

A secondary finding of this study is that increasing amounts of postoperative crystalloid administration were independently associated with the occurrence of complications and there was a non-significant trend suggesting that patients who had a major complication received more IVF prior to the complication being diagnosed. There are three potential explanations for this finding. Increased IVF administration may have led to fluid overload and consequent development of complications. (188) Conversely, IVF may have been administered as a consequence of the complication or to treat intraoperative hypovolaemia, which itself could have predisposed patients to developing a complication. (221, 236) Lastly, postoperative fluid requirement may be a marker of adverse outcomes in this setting rather than directly related to the occurrence or treatment of a complication. This observational study is unable to determine which of these hypotheses is most accurate but it is important to acknowledge that the best clinical outcome was associated with minimal IVF administered perioperatively – a finding which is supported by studies in various surgical settings. (72, 317) A recent review of the data from the European ERAS group has also shown perioperative fluid restriction to be independently associated with decreased complications. (318)

Although intraoperative fluid restriction was able to be uniformly implemented, a subset of patients in this study received more IVF postoperatively. Higher quantities of IVF may have been required postoperatively to compensate for undetected
intraoperative hypovolaemia in some patients. The results indicate that this subset of vulnerable patients cannot be determined by ASA scores as observed differences in postoperative IVF administration were not statistically significant. Wenkui et al. recently demonstrated that 28% of patients undergoing major colorectal surgery in their trial were hypoperfused following intraoperative fluid restriction.(221) The potential for hypovolaemia with restrictive, fixed-volume regimens has also been described by Futier et al. and has previously been shown to be independently associated with the development of complications.(237, 319)

This study cannot answer whether intraoperative fluid restriction is the ideal fluid regimen due to the lack of a comparator group. This subject has been addressed in previous randomised trials and lower fluid volumes have been shown in most trials to be superior to so-called liberal fluid administration.(43, 72, 215) However, the fact that some patients in this study required greater volumes of postoperative IVF suggests a deficiency in fixed-volume regimens, high or low. Varadhan et al. have demonstrated that fluid imbalance as a result of too little or too much fluid leads to adverse outcomes.(192) GDFT represents a possible solution as it provides physiologically-guided, individualised fluid administration to optimise haemodynamics and tissue perfusion. GDFT is supported by multiple randomised trials though its current role within an ERAS protocol is unclear.(294, 312) Moreover, as currently practiced, GDFT is largely feasible only within the intraoperative phase. Further studies are needed comparing fluid restriction to GDFT to determine the ideal fluid regimen.

This study is limited by its retrospective nature and can only generate hypotheses regarding the link between administered fluid amounts and observed clinical outcomes. Moreover, whilst this study has explored quantities of IVF administered, it
has not accounted for differences in the composition of individual fluids and their resultant effects on serum electrolytes as previous work has shown that dysnatraemia is associated with increased mortality.(320) Another weakness of the study is that daily weights and losses were unable to be accurately noted due to missing data and as such, fluid balance was unable to be measured. Similarly, since the IDC was removed on post-operative day one, urine output could not be serially measured.

This study was able to demonstrate the feasibility of intraoperative fluid restriction and evaluate its relationship with postoperative fluid management within an otherwise standardised and optimised perioperative care protocol. It has shown that intraoperative fluid restriction can be uniformly employed in ASA 1–3 patients undergoing elective colectomy within an ERAS protocol without the need for compensatory postoperative IVF. This strategy could serve as a baseline against which other fluid regimens could be trialled and also represents one theory of current best practice. Increased postoperative IVF administration was associated with adverse outcomes, which may reflect a causative relationship or be an early marker for poorer outcomes. A subset of patients, who are not able to be identified by ASA scores, may benefit from GDFT which deserves further investigation in this context.
4. Goal-Directed Fluid Therapy – A survey of anaesthetists in the UK, USA, Australia and New Zealand

4.1 Introduction

In Chapter three, it was demonstrated that intraoperative fluid restriction can be implemented uniformly in patients undergoing elective colectomy within an ERAS protocol. However, even though intraoperative fluid restriction can be implemented uniformly, in the wider context of perioperative fluid therapy it is not known whether it should be implemented since another fluid strategy – GDFT – has also been proposed as potentially beneficial. An increasing body of work has now highlighted the importance of physiologically-guided, individualised fluid administration in keeping with the broad principles recommended by Moore and Shires over 40 years ago.(184, 264)

GDFT therapy primarily involves the administration of intravenous fluids to optimise pre-defined, patient-specific clinical proxies of tissue perfusion.(264) The individual parameters used to guide therapy are measures of cardiovascular function and vary depending on the monitoring system used.(264) In practice, GDFT involves repeated administration of small boluses of intravenous fluids – often colloids – until a certain target or plateau is reached. A baseline infusion of crystalloids is typically given.

A number of randomised trials and subsequent meta-analyses in various surgical settings have shown that GDFT confers clinical benefits.(72, 200, 241, 242, 247, 294, 297) However, some authors have expressed reservations regarding the proposed benefits of GDFT for all patients. The criticisms include a paucity of trials within an optimised perioperative care environment and no comparison to
intraoperative fluid restriction, which is also recognised as beneficial in a similar cohort of patients. (71, 72, 321, 322) As will be shown in depth in Chapter five, there are several important unanswered questions in the context of GDFT in colorectal surgery. (312) Moreover, questions persist regarding the best monitoring system, the ideal intraoperative fluid and clinical situations when GDFT is appropriate. (18, 264, 312) Therefore, there may be clinical and academic equipoise regarding the proposed benefits or otherwise of GDFT.

It is thus important to assess the current practice and attitudes of clinicians and to identify barriers that may prevent the future implementation of evidence-based practice. (305, 323) A survey would also help determine whether the clinical environment may allow future studies pertaining to fluid administration to be conducted. Therefore, we conducted a survey of anaesthetists nationally and internationally to investigate the uptake of GDFT across Australasia, the United Kingdom (UK) and the USA. This survey was not limited to colorectal surgery alone as it sought to understand the place of GDFT across a wide domain of clinical practice and did not wish to exclude potential respondents who may practice in colorectal surgery without this being their primary subspecialty interest.

4.2 Methods

4.2.1 Study design

This study was a cross-sectional survey of randomly selected, consenting anaesthetists from the United Kingdom, America, Australia and New Zealand.

4.2.2 Survey creation

An electronic survey was created using a commercially available Internet-based service. (310) Questions were based upon matters of clinical interest. Discrete
choices and free text fields were provided. An ordinal Likert scale was also used for applicable questions. The questions are listed in Table 12.

4.2.3 Study set-up

This survey was designed in consultation with the Australia and New Zealand College of Anaesthetists (ANZCA) Trials group. Following approval of content by this organisation, ethical approval was sought and obtained. The final version of the survey was then forwarded to the research coordinators of the AAGBI and the ASA. Permission was sought from these organisations as well as ANZCA to administer this survey to their members.

4.2.4 Conduct of study

The survey was administered electronically to 2000 randomly chosen members of the AAGBI, 2000 members of the ASA and to 500 randomly chosen members of the ANZCA. All organisations stipulated this as the maximum acceptable sample size for the survey and hence fewer ANZCA members were approached. Individuals were invited to participate via an email with a covering letter explicitly stating the aim of the study. A hyperlink was provided to access the survey online. The individuals were randomly chosen by the respective organisations and the study investigator had no influence on the sample characteristics. An attempt was made to distribute the survey to individuals who had not been surveyed recently to minimise survey ‘fatigue.’ All respondents remained anonymous to the study investigator. One reminder was sent to all non-responders four weeks after the first invitation. The data collection phase of the survey was declared as closed after a further two weeks, thereby providing a total of six weeks for respondents to participate. The results were subsequently collated and subjected to analysis.
4.2.5 Statistical analysis

A two-tailed Fisher’s exact test was used to assess categorical outcomes. A $p$ value of less than 0.05 was defined as statistically significant a priori.

Table 12: Survey questions

<table>
<thead>
<tr>
<th>Questions</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which country do you work in?</td>
<td>Tertiary Hospital/District (Community)Hospital/ Private practice</td>
</tr>
<tr>
<td>What is your place of practice? (Choose as many as applicable)</td>
<td>Abdominal Surgery/Non-abdominal general surgery/Orthopaedic surgery/Urology/Cardiothoracic surgery/Obstetrics/ Gynaecology/Vascular Surgery/Neurosurgery/Otorhinolaryngology/Ophthalmology/Plastic Surgery/Paediatric Surgery/ Trauma/ Burns</td>
</tr>
<tr>
<td>What is your subspecialty interest? (up to three choices)</td>
<td>Trainee/Consultant &lt; 5 years/Consultant 5–10 years/Consultant &gt; 10 years</td>
</tr>
<tr>
<td>For adult patients having major elective surgery...</td>
<td></td>
</tr>
<tr>
<td>What is your preferred intraoperative crystalloid fluid?</td>
<td>Normal saline/Balanced salt solution/Dextrose saline/No preference</td>
</tr>
<tr>
<td>What is your preferred intraoperative colloid fluid?</td>
<td>Succinylated gelatin/Tetrastarch/Pentastarch/Hetastarch/ Albumin/Nil/No preference/Other</td>
</tr>
<tr>
<td>What is your preferred intraoperative pressor? (Please state type)</td>
<td></td>
</tr>
<tr>
<td>For adult patients undergoing major elective surgery, do you use Goal-Directed Fluid Therapy?</td>
<td>Always/ Sometimes/ Never</td>
</tr>
<tr>
<td>If you use goal directed fluid therapy sometimes, when? (Choose as many as applicable)</td>
<td>Major surgery/Patients with significant comorbidities/Particular operations (state type)/Depending on Instrument availability/Random/Other</td>
</tr>
<tr>
<td>If yes, what kind of surgery do you use goal directed fluid therapy in? (Choose as many as applicable)</td>
<td>Abdominal Surgery/Non-abdominal general surgery/Orthopaedic surgery/Urology/Cardiothoracic surgery/Obstetrics/Gynaecology/Vascular Surgery/Neurosurgery/Otorhinolaryngology/Ophthalmology/Plastic Surgery/Paediatric Surgery/Trauma/ Burns</td>
</tr>
<tr>
<td>What are your preferred tools to conduct Goal Directed Fluid Therapy? (Choose up to 3)</td>
<td>ODM/PPV monitors/SVV monitors/LiDCO/PAC/SvO2/ PVI</td>
</tr>
<tr>
<td>If you never use goal directed fluid therapy, why? (Choose as many as applicable)</td>
<td>Lack of resources/Nil advantage perceived/Too labour intensive/ Unsuitable patients/Lack of experience with instruments</td>
</tr>
<tr>
<td>If existing barriers were removed (e.g. lack of resources/training), would you like to use Goal Directed Fluid Therapy?</td>
<td>Yes/No/Undecided</td>
</tr>
</tbody>
</table>

**ODM**: Oesophageal Doppler monitor; **PPV**: Pulse pressure variation; **SVV**: Stroke volume variation; **LiDCO**: Lithium dilution coefficient; **PAC**: Pulmonary artery catheter; **SvO2**: Venous oxygen saturations; **PVI**: Pleth variability index
4.3 Results

4.3.1 Response rate and demographics

The demographic characteristics of respondents and the response rates are presented in Table 13. The response rates in the UK and AUS/NZ were 35% and 36% respectively. The response rate in the USA was 9%, thereby limiting the validity of any deductions from these data. Amongst responders, the survey completion rate was high across all three regions (UK: 94%; AUS/NZ: 89%). The two commonest subspecialty interests were orthopaedic surgery (AUS/NZ: 76 (46%); UK: 240 (37%)) and abdominal surgery (AUS/NZ: 71(43%); UK: 300 (46%)).

Table 13: Respondent characteristics

<table>
<thead>
<tr>
<th></th>
<th>AUS/NZ n=180</th>
<th>UK n=708</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>36%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Place of practice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary Hospital-District Hospital</td>
<td>122 69</td>
<td>360 51</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Private</td>
<td>34 19</td>
<td>377 54</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Practice</td>
<td>68 38</td>
<td>89 13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Experience</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trainee</td>
<td>2 1</td>
<td>168 24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Consultant &lt;5 years</td>
<td>27 15</td>
<td>161 23</td>
<td>0.02</td>
</tr>
<tr>
<td>Consultant 6–10 years</td>
<td>28 16</td>
<td>98 14</td>
<td>0.63</td>
</tr>
<tr>
<td>Consultant &gt;10 years</td>
<td>122 68</td>
<td>269 39</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Two-tailed Fisher’s Exact Test

4.3.2 Intraoperative fluid preferences

Intraoperative fluid preferences are as per Table 14. The two most favoured pressors in the UK and AUS/NZ were metaraminol (UK: 281 (42%); AUS/NZ: 102 (59%)) and phenylephrine (UK: 142 (22%); AUS/NZ: 36 (21%)).
Table 14: Intraoperative fluid preferences

<table>
<thead>
<tr>
<th>Crystalloid</th>
<th>AUS/NZ n=174</th>
<th>UK n=692</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% Saline</td>
<td>10 (6%)</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Balanced Salt Solution</td>
<td>162 (93%)</td>
<td>662 (96%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Colloid</th>
<th>AUS/NZ n=174</th>
<th>UK n=692</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylated gelatine</td>
<td>43 (24%)</td>
<td>292 (42%)</td>
</tr>
<tr>
<td>Tetrastarch</td>
<td>30 (17%)</td>
<td>98 (14%)</td>
</tr>
<tr>
<td>Pentastarch</td>
<td>29 (16%)</td>
<td>50 (7%)</td>
</tr>
<tr>
<td>Hetastarch</td>
<td>29 (16%)</td>
<td>124 (18%)</td>
</tr>
<tr>
<td>Albumin</td>
<td>14 (8%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>No preference</td>
<td>26 (15%)</td>
<td>98 (14%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (4%)</td>
<td>29 (4%)</td>
</tr>
</tbody>
</table>

4.3.3 Use of Goal-Directed Fluid Therapy

The use of GDFT is shown in Figure 4. GDFT use was significantly more common in the UK as compared to AUS/NZ (p<0.01). In AUS/NZ, GDFT was most commonly utilised in abdominal surgery (n=60; 80%), followed by orthopaedic surgery (n=27; 36%). In the UK, GDFT was most commonly utilised in abdominal surgery (UK: n=428 (89%)), followed by vascular surgery (UK: n=146 (30%)).

![Figure 4](image.png)

Figure 4: Do you use Goal-Directed Fluid Therapy? USA vs. UK, p=0.36; USA vs. NZ, p< 0.01; UK vs. NZ, p<0.01
Table 15: Situations when Goal-Directed Fluid Therapy is used

<table>
<thead>
<tr>
<th>Indication</th>
<th>AUS/NZ n=87</th>
<th>UK n=523</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Major Surgery</td>
<td>50</td>
<td>69</td>
</tr>
<tr>
<td>Significant Comorbidities</td>
<td>51</td>
<td>70</td>
</tr>
<tr>
<td>Specific Operations</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Instrument availability</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Random</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The situations when GDFT is utilised and preferred tools to conduct GDFT are shown in Table 15 and 16 respectively. The commonest reasons stated for not using GDFT were either lack of availability of monitoring tools (AUS/NZ: 57 (70%); UK: 94 (64%)) or a lack of experience with instruments (AUS/NZ:43 (53%); UK: 51 (35%)). A subset of respondents cited “nil advantage perceived” as the reason for not using GDFT (AUS/NZ: 22(27%); UK: 45 (30%)). Enthusiasm towards GDFT in the absence of existing barriers (e.g. lack of equipment or experience) is shown in Figure 5.

Table 16: Preferred tools for Goal-Directed Fluid Therapy

<table>
<thead>
<tr>
<th>Tools</th>
<th>AUS/NZ n=78</th>
<th>UK n=519</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODM</td>
<td>11</td>
<td>362</td>
</tr>
<tr>
<td>PPV</td>
<td>26</td>
<td>97</td>
</tr>
<tr>
<td>SVV</td>
<td>21</td>
<td>71</td>
</tr>
<tr>
<td>LiDCO</td>
<td>1</td>
<td>93</td>
</tr>
<tr>
<td>PAC</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>SvO2</td>
<td>12</td>
<td>88</td>
</tr>
<tr>
<td>PVI</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

**ODM**: Oesophageal doppler monitor; **PPV**: Pulse pressure variation; **SVV**: Stroke volume variation; **LiDCO**: Lithium dilution coefficient; **PAC**: Pulmonary artery catheter; **SvO2**: Venous oxygen saturation; **PVI**: Pleth variability index
4.3.4 Data from the USA

The respondents from the USA indicated a preference towards GDFT in abdominal surgery (n=97; 80%) with similar barriers to GDFT as described in other regions such as lack of availability of tools (n=19; 59%), lack of experience (n=13; 40%) and nil perceived advantage (n=13; 40%). The most favoured pressor in the USA was phenylephrine (68; 40%), followed by ephedrine (41; 24%).

4.4 Discussion

This survey of 1067 anaesthetists from the UK, AUS/NZ and the USA reveals important differences in practice with regards to intraoperative fluid therapy and GDFT specifically. The response rates were moderate or low, especially in the USA, and it is likely that the present data represents views of a self-selected group among the anaesthetists who were randomly invited to participate. Such selection could be based on strong positive or negative views on GDFT. Nevertheless, certain
observations can be made and hypotheses generated regarding the interest in and barriers to GDFT in the UK and AUS/NZ. The poor response rate from the USA limits the validity of any statements regarding practice in this region.

The use of GDFT seems to be significantly less prevalent in AUS/NZ compared to the UK amongst respondents in this survey. The majority of the respondents were involved in major abdominal surgery and orthopaedic surgery and used GDFT in patients with significant comorbidities. The ODM is the most commonly utilised instrument in the UK with significant variation in preferences in other regions. The most significant barriers to conducting GDFT were either a lack of availability of monitoring tools or a lack of experience with instruments. Even though a proportion of respondents from all regions remain unconvinced of the benefits of GDFT, there was significant enthusiasm overall towards trialling GDFT if barriers were to be removed.

The use of GDFT was most common in the UK which may have been made possible by governmental endorsement and funding of the ODM specifically with demonstrated cost-effectiveness.(298, 299) For clinicians, the recently published GIFTASUP guidelines which recommend mandatory use of GDFT in major abdominal surgery may have also provided further impetus.(303) Moreover, a significant portion of the evidence supporting GDFT originates from the UK.(241, 247, 287) The recent guidelines from the European ERAS group have also shown enthusiasm towards GDFT and the ODM and, as ERAS protocols are instituted across the UK, GDFT has been integrated into practice as well.(21, 324, 325) This has likely led to the emergence of the ODM as the preferred tool to conduct GDFT in the UK. The increasing clinical uptake of the ODM and GDFT may potentially erode
equipoise regarding this subject in the region and could make the conduct of further prospective studies difficult and/or subject to bias.

In contrast, the principles of optimised perioperative care have shown reduced penetrance in AUS/NZ with persisting scepticism regarding benefits. In AUS/NZ, there appears to be clinical equipoise with regards to tools for GDFT. There have also been no studies of GDFT in AUS/NZ and a potential change in practice may require prospective studies conducted in this region so that they are more likely to be considered locally relevant. The prevalent environment of academic and clinical equipoise in this region is likely to be suitable for the conduct of prospective studies to address outstanding questions.

The barriers identified to the use of GDFT appear eminently solvable especially if the observed benefits from trials are replicated in clinical practice. Many of the instruments used to conduct GDFT are simple to use and the learning curve for the ODM can be overcome after 12 insertions. However, it should be noted that in the context of abdominal surgery, restrictive fluid regimens have also shown similar benefits to GDFT and the majority of the trials investigating GDFT have not been conducted in an environment of standardised, optimised perioperative care.

A proportion of people from all the regions surveyed remain sceptical regarding the proposed benefits of GDFT. This is justified to an extent as important questions remain unanswered, such as efficacy in settings where fluid restriction has been shown to be beneficial. Nonetheless, it is interesting to note that in the absence of barriers, a high proportion of respondents would be willing to consider GDFT into their practice. This suggests that future randomised trials or selective clinical implementation of GDFT remain feasible and are required.
In conclusion, there are important differences in fluid administration and the use of GDFT between anaesthetists from the UK and AUS/NZ. The identified barriers can potentially be overcome and though some clinicians remain unconvinced, the clinical environment is conductive to future studies with significant interest in utilising GDFT in clinical practice.
5. Oesophageal doppler-guided fluid administration in colorectal surgery – Critical appraisal of the methodology of published clinical trials

5.1 Introduction

In the previous chapter, the clinical interest in GDFT and the popularity of the ODM was demonstrated amongst some survey respondents. The latter is a reflection of the fact that the ODM is supported by the largest evidence base to date as compared to the other tools for GDFT discussed in Chapter one. Chapter two and four also showed that for some respondents, clinical equipoise remains with regards to the place of intravenous fluid therapy within modern perioperative settings. In Chapter four, it was also postulated that the combination of prevalent ambivalence and clinical interest regarding GDFT and the ODM in AUS/NZ could be beneficial as it may provide a suitable environment to conduct further studies. Previously published studies have dictated current policy and any attempt at answering outstanding questions by designing new studies requires detailed knowledge regarding the published trials.

RCTs exploring ODM-guided fluid administration in Abdominal Surgery have shown benefits in reducing hospital LOS and decreasing post-operative morbidity.(243, 244, 247, 288) There are multiple meta-analyses which summarise data from the same RCTs and have concluded that ODM-guided intraoperative fluid administration in abdominal surgery confers clinical benefits.(72, 294, 295)

Thus, as discussed in chapter one and three, two intraoperative fluid strategies have been proposed as optimal: fluid restriction and GDFT. However, these strategies are somewhat contradictory since patients treated as per ODM measurements receive quantities of intravenous fluid which are greater than those
recommended in restrictive regimens. Critical analysis of the literature comparing fixed-volume regimens has revealed important gaps in knowledge that must be acknowledged when determining the superiority of restrictive fluid regimens over liberal fluid administration. Similarly, the evidence base which underpins the current recommendations around the use of ODM in colorectal surgery may be heterogeneous and suffers from notable deficiencies such as a lack of homogenous perioperative care and no direct comparison of ODM-guided fluid administration to intraoperative fluid restriction. Other authors, including the Auckland Enhanced Recovery After Surgery group, have previously commented on the limitations of the literature but this has never been approached in a systematic way. It is therefore important to qualitatively review the methods and findings from each relevant trial to determine whether the evidence from published trials justifies the current recommendations and whether ODM-guided fluid management constitutes best practice in colorectal surgery. Any outstanding questions can then also guide the design of future studies.

5.2 Methods

5.2.1 Selection of eligible trials

A systematic literature search of Medline (1966 to January 2010 via Ovid), Embase (1974 to January 2010 via Ovid) and The Cochrane Library (2009) was conducted. The search strategy consisted of a highly sensitive filter for detection of RCTs as well as relevant keywords (major surgery; abdom* surgery; colon resect*; colon* surgery; rect* resect*; rect*; colorect* resect*; surgery; colorect* surgery; crystall* fluid; colloid* fluid; colloid* administration; crystall* administration; fluid titration; Doppler; oesophageal doppler monitoring) without any language restriction. Exploded medical subject headings and relevant combinations of these terms were
searched for. Reference lists of relevant articles were screened for additional trials. Reference lists of published reviews were also screened for eligible trials. Only published randomised studies investigating ODM-guided intraoperative fluid administration in abdominal surgery were eligible for inclusion. Any disagreement was resolved by consultation with senior authors.

5.2.2 Data recorded

The sample size of each trial, patient characteristics, operative characteristics and outcomes were recorded. The trial quality was judged using the Jadad scale (328) and other measures of methodological rigour (allocation concealment; randomisation; power calculation; blinding; intention to treat). A funnel plot was also constructed to detect any publication bias. The presence or absence of relevant aspects of perioperative care as mentioned in the publications was noted. Particular attention was given to intraoperative fluid administration and administered fluid volumes.

5.3 Results

The literature search identified ten randomised trials (200, 241, 243, 244, 247, 283, 286-289) Four of these were not conducted in patients undergoing bowel surgery (200, 241, 286, 287) whilst one did not use ODM (283) Hence five RCTs were included for analysis (243, 244, 247, 288, 289) Four of these were specific to colorectal surgery (243, 244, 247, 289) whilst one trial included patients undergoing urological, gynaecological and general surgical procedures (288) This trial was included for analysis as it has been included in all published meta-analyses, thereby contributing to the current recommendations regarding use of ODM in colorectal surgery. One included trial was a three-armed study comparing standard fluid
administration with ODM-guided crystalloid and ODM-guided colloid fluid regimens. (289)

5.3.1 Summary of eligible trials

Table 17 summarises the five included trials. Four of the five trials were specific to colorectal surgery, though the exact procedures were not specified by Conway. Information on laparoscopic surgery was provided by three of the trials and very few patients overall underwent laparoscopic colonic surgery. (244, 247, 289) The distinction between colonic and rectal cases was made in three trials (244, 247, 289) with data on stoma formation provided by two trials. (244, 289) The median American Society for Anesthesiologists (ASA) score in all trials was two though the trial by Senagore provided no information on ASA nor any indication of preoperative cormobidity. (289) This same trial did not report whether study groups were comparable at baseline. (289) Four trials had a primary endpoint of LOS (244, 247, 288, 289) and one trial was powered for detecting an increase in cardiac output (CO). (243) The key results of each trial are summarised in Table 17. The amounts of fluid administered are displayed in Figure 6 for four of the trials. Senagore administered 2850mL of Ringer’s lactate to the “Standard” group, 3800mL of Ringer’s lactate to the ODM-guided crystalloid group and 3300mL of fluid (Ringer’s lactate and 6% hydroxyethyl starch) to the ODM-guided colloid group. (289) The study methodology has been critiqued in Table 18 with scores as per the Jadad scale. Senagore et al. did not explicitly mention adherence to intention to treat principles. (41) The trials by Wakeling and Noblett clearly outlined any deviations from treatment post-randomisation. (25, 26) None of the other trials specified whether there were any intraoperative breaches of the fluid administration protocol. There was no evidence of publication bias.
## Table 17: Included RCT details

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sample size</th>
<th>All Colorectal</th>
<th>Mean Duration (mins)</th>
<th>Lap Cases</th>
<th>Rectal cases</th>
<th>Stoma</th>
<th>Median ASA</th>
<th>ERAS</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan (288)</td>
<td>2002</td>
<td>100</td>
<td>No</td>
<td>234</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>No</td>
<td>LOS</td>
<td>Cx, Intraoperative cardiac variables, Tx, Solid Diet, N, V</td>
<td>ODM- ↓LOS, ↑CO, ↑SV, ↑FTc, ↓N+V, ↓Tx, Earlier solid diet</td>
</tr>
<tr>
<td>Conway (243)</td>
<td>2002</td>
<td>57</td>
<td>Yes</td>
<td>137</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>No</td>
<td>CO</td>
<td>Cx, Critical Care Stay, LOS, Solid Diet, Amount of Fluid</td>
<td>ODM- ↑CO, ↑SV, ↑FTc, ↑colloid given, ↓Critical Care Stay</td>
</tr>
<tr>
<td>Wakeling (244)</td>
<td>2005</td>
<td>128</td>
<td>Yes</td>
<td>153</td>
<td>0</td>
<td>64</td>
<td>50</td>
<td>2</td>
<td>No</td>
<td>LOS</td>
<td>Cx, Intraoperative Cardiac Variables, Amount of Fluid, Tx Solid Diet, Flatus, Bowel Motion, CRP, Cytokines, QoL</td>
<td>ODM- ↓LOS, ↓Cx, ↓colloid given, Earlier solid diet, Earlier flatus</td>
</tr>
<tr>
<td>Noblett (247)</td>
<td>2006</td>
<td>108</td>
<td>Yes</td>
<td>158</td>
<td>26</td>
<td>53</td>
<td>–</td>
<td>2</td>
<td>No</td>
<td>LOS</td>
<td>Cx, Intraoperative Cardiac variables, Critical Care Stay, Flatus, Cytokine release</td>
<td>ODM- ↓LOS, ↓Cx, ↑CO, ↑SV, ↑FTc, ↓cytokine release, Earlier solid diet</td>
</tr>
<tr>
<td>Senagore (289)</td>
<td>2009</td>
<td>64</td>
<td>Yes</td>
<td>144</td>
<td>64</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>Yes</td>
<td>LOS</td>
<td>Cx, Operative time, Amount of Fluid,</td>
<td>ODM- ↑LOS, ↑Cx, ↑colloid given</td>
</tr>
</tbody>
</table>

**Lap**: Laparoscopic Colorectal Surgery; **ASA**: American Society of Anesthesiologists Score; **ERAS**: Enhanced Recovery After Surgery; **LOS**: Length of Stay; **Tx**: Blood Transfusion; **N**: Nausea; **V**: Vomiting; **Cx**: Complications; **ODM**: Oesophageal Doppler Monitoring; **CO**: Cardiac Output; **SV**: Stroke Volume; **FTc**: Corrected Flow Time; **QoL**: Quality of Life; –: No information available; ↑: Improved/Increased; ↓: Decreased
Table 18: Summary of study quality

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Jadad Score</th>
<th>Power calculation ( ^{a \text{ prior}} )</th>
<th>Randomisation</th>
<th>Allocation Concealment</th>
<th>Blinding of Intervention</th>
<th>Binding of Assessment</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan (288)</td>
<td>2002</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Conway (243)</td>
<td>2002</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Wakeling (244)</td>
<td>2005</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Noblett (247)</td>
<td>2006</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Senagore (289)</td>
<td>2009</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
</tr>
</tbody>
</table>

**ITT:** Intention to treat; –: Not explicitly stated

---

![Graph showing perioperative fluid amounts](image)

Figure 6: Perioperative fluid amounts

### 5.3.2 Preoperative and intraoperative care

Table 19 summarises the preoperative and intraoperative management of each trial. The most recent RCT was conducted within an ERAS setting.(289) Bowel preparation was utilised in three trials (243, 244, 289) with no information provided regarding its use in the other two trials.(247, 288) Preoperative IVF was administered in four trials (244, 247, 288, 289) with no information provided in the other trial.(243) Details regarding perioperative IVF administration were provided by
three of the trials (244, 288, 289) though only one trial (which did not provide details) stated whether this fluid was accounted for in the overall calculations regarding total IVF administered. (247) The ‘intraoperative’ period was not defined in any of the trials and it is unclear whether this constitutes the operation alone or any postoperative stay prior to ward transfer (e.g. Post Anaesthetic Care Unit) as well. Intraoperative epidural analgesia was mentioned as being employed in one trial. (247)
Table 19: Preoperative and Intraoperative Care

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Bowel Prep</th>
<th>Preop IVF (Type)</th>
<th>Anaesthesia described</th>
<th>Intraop Period Defined</th>
<th>Intraop Epidural</th>
<th>Invasive BP measurement</th>
<th>CVP measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan (288)</td>
<td>2002</td>
<td>–</td>
<td>Yes (5ml/kg Lactated Ringer’s Solution)</td>
<td>Yes</td>
<td>–</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Conway (243)</td>
<td>2002</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
<td>–</td>
<td>No</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Wakeling (244)</td>
<td>2005</td>
<td>Yes</td>
<td>Yes (1-2L Hartmann’s Solution)</td>
<td>Yes</td>
<td>–</td>
<td>No</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Noblett (247)</td>
<td>2006</td>
<td>–</td>
<td>Yes (–)</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Senagore (289)</td>
<td>2009</td>
<td>Yes</td>
<td>Yes (5ml/kg Lactated Ringer’s)</td>
<td>No</td>
<td>–</td>
<td>No</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Bowel Prep:** Mechanical Bowel Preparation; **Preop:** Preoperative; **IVF:** Intravenous Fluids; **Intraop:** Intraoperative; **BP:** Blood Pressure; **CVP:** Central Venous Pressure; -: No information available

5.3.3 Intraoperative fluid management

Table 20 summarises the intraoperative fluid management in both the intervention and control groups in each trial.

Table 20: Intraoperative Fluid Management Strategies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Control Fluid Algorithm</th>
<th>ODM algorithm</th>
<th>Bolus Fluid</th>
<th>ODM Colloid (Type)</th>
<th>Control Colloid (Type)</th>
<th>ODM Crystalloid (Type)</th>
<th>Control Crystalloid (Type)</th>
<th>Indications for additional fluid/ blood</th>
<th>Inotrope/ Pressor (Details)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan (288)</td>
<td>2002</td>
<td>Yes</td>
<td>FTc&lt; 0.35 and SV</td>
<td>Colloid/ Crystalloid</td>
<td>Yes (6% HES)</td>
<td>Yes (6% HES)</td>
<td>Yes (Ringer’s lactate)</td>
<td>Yes (–)</td>
<td>Yes</td>
<td>Yes (–)</td>
</tr>
<tr>
<td>Conway (243)</td>
<td>2002</td>
<td>No</td>
<td>FTc. 0.35 and SV- no initial bolus</td>
<td>Colloid</td>
<td>Yes (6% HES)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Yes (–)</td>
</tr>
<tr>
<td>Wakeling (244)</td>
<td>2005</td>
<td>Yes</td>
<td>CVP and SV</td>
<td>Colloid</td>
<td>Yes (Haemacell®/ Gelofusin®)</td>
<td>Yes (–)</td>
<td>Yes (–)</td>
<td>Yes (–)</td>
<td>Yes (–)</td>
<td>–</td>
</tr>
<tr>
<td>Noblett (247)</td>
<td>2006</td>
<td>No</td>
<td>FTc&lt; 0.35 and SV- initial bolus</td>
<td>Colloid</td>
<td>Yes (Volplex®)</td>
<td>Yes (Volplex®)</td>
<td>Yes (–)</td>
<td>Yes (–)</td>
<td>Yes (–)</td>
<td>Yes (–)</td>
</tr>
<tr>
<td>Senagore (289)</td>
<td>2009</td>
<td>Yes</td>
<td>SV dependent</td>
<td>Colloid/ Crystalloid</td>
<td>Yes (6% HES)</td>
<td>No</td>
<td>Yes (Ringer’s lactate)</td>
<td>Yes (Lactated Ringer’s)</td>
<td>Yes</td>
<td>Yes (–)</td>
</tr>
</tbody>
</table>

**ODM:** Oesophageal Doppler Monitoring; **FTc:** Corrected Flow Time; **SV:** Stroke Volume; **HES:** Hydroxyethyl Starch; **CVP:** Central Venous Pressure; -: No information available
5.3.3.1 Intervention Group

Only Conway discussed calibration of the ODM. All trials used different, though similar, algorithms for ODM-guided fluid administration. Four trials administered colloids as guided by ODM measurements though Gan also administered crystalloids after administering 20ml/kg of 6% hydroxyethyl starch. The colloids used for ODM-guided fluid administration were either 6% hydroxyethyl starch (243, 288, 289) or polygeline infusion solutions.(244, 247)

5.3.3.2 Control Group

Two trials did not standardise fluid administration in the control group (243, 247) whilst two trials employed a standardised algorithm but also allowed anaesthetists to administer fluids ‘as clinically indicated’. (288, 289) No trials employed intraoperative fluid restriction in the control group. Two trials detailed the colloids used for fluid administration in control group patients.(247, 288) Details regarding crystalloid fluids were specified in two trials (288, 289) and only one trial specified any policy for administration of blood products.(288)

5.3.4 Vasopressors

One study provided detail on vasopressor use in the methods (247) with other studies either mentioning it in the methods(289) or discussion(288) , evaluating it as an endpoint(243) or not mentioning vasopressor use at all.(244)

5.3.5 Postoperative management

Table 21 summarises relevant aspects of postoperative management. The postoperative period was not clearly defined in any of the trials. One trial provided details on postoperative fluid management.(289) Two trials mentioned administration of postoperative fluids though no details were provided.(244, 247) Two trials did not
discuss postoperative fluid management. (243, 288) Three trials mentioned the use of a post-operative epidural. (244, 247, 288) Only Senagore mentioned other aspects of postoperative care such as early ambulation, removal of in-dwelling catheters etc.

Table 21: Postoperative Care

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Post-op Period Defined</th>
<th>Post-op Fluids (Details)</th>
<th>Post-op Epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan</td>
<td>2002</td>
<td>no</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Conway</td>
<td>2002</td>
<td>no</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Wakeling</td>
<td>2005</td>
<td>no</td>
<td>Yes (–)</td>
<td>Yes</td>
</tr>
<tr>
<td>Noblett</td>
<td>2006</td>
<td>no</td>
<td>Yes (–)</td>
<td>Yes</td>
</tr>
<tr>
<td>Senagore</td>
<td>2009</td>
<td>no</td>
<td>Yes (Ringer’s lactate)</td>
<td>No</td>
</tr>
</tbody>
</table>

Post-op: Postoperative; –: No information available

5.3.6 Outcomes analysis

Three trials concluded that ODM-guided fluid administration decreased hospital LOS (244, 247, 288) but only two of these specified discharge criteria (244, 247) as shown in Table 22. One trial found ODM-guided colloid administration increased LOS and increased complications. (289) Complications were defined in three trials (244, 247, 288) though only two trials evaluated strictly fluid-related complications. (247, 288) None of the trials reported change in weight, fluid balance or any measure of diuresis.

Table 22: Outcomes Analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Change in TBW</th>
<th>Fluid Balance</th>
<th>Diuresis</th>
<th>d/c criteria specified</th>
<th>Cx definitions used</th>
<th>Cx fluid related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan</td>
<td>2002</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Conway</td>
<td>2002</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Wakeling</td>
<td>2005</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Noblett</td>
<td>2006</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Senagore</td>
<td>2009</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

TBW: Total Body Weight; d/c: Discharge; Cx: Complications; –: No information available
5.4 Discussion

The use of ODM in colonic surgery has been recommended on the basis of three meta-analyses which have summarised data from four well-designed RCTs composed of 393 patients in total. (72, 243, 244, 247, 288, 294, 295) One other RCT of 64 patients has been subsequently published in this area which reports an increased length of stay and increased complications in patients receiving ODM-guided colloid administration. (289) Despite this result, the overall consensus is that ODM-guided intraoperative fluid administration reduces hospital LOS and postoperative morbidity as a result of optimised cardiac indices. However, recent advances in perioperative care and lack of standardisation between existing studies significantly limits the generalisability of the evidence.

The RCTs analysed in this paper have not made a clear distinction between colonic and rectal resections when reporting results, even though there are significant differences in expected outcomes with regards to hospital stay and morbidity between colonic and rectal resections. (329, 330) Rectal resections can require bowel preparation leading to dehydration and electrolyte derangement. (93) Only the trial by Senagore makes the distinction between colonic and rectal resections by including only colonic resections in the study population. (289) Rectal resections are also often accompanied by the creation of a stoma which may affect fluid balance in high output states. This may, in turn, require a greater quantity of postoperative fluids and prolong day-stay but has not been adequately addressed in the published trials.

The majority of included patients in all the trials were ASA two patients with low baseline perioperative risk. Similar patients have also benefited from intraoperative fluid restriction. (43, 215) Only one trial has been conducted within an ERAS setting.
and there has been no comparison of ODM-guided fluid administration with intraoperative fluid restriction. Exact intraoperative fluid administration using ODM within an otherwise optimised setting may not confer additional clinically significant benefits in patients with low baseline perioperative risk as suggested by the trial of Senagore. To the author's knowledge, no investigation or subgroup analysis of ODM-guided fluid administration has been conducted specifically in ASA 3 and 4 patients undergoing colorectal surgery.

The available data also suffer from a lack of precise definitions. Neither the intraoperative or postoperative period are clearly defined. There is thus potential for crossover between periods especially during patient transit in postoperative recovery units. This issue has also been identified when assessing studies comparing liberal and restrictive fluid administration.(223) Data regarding fluid administration in the preoperative or postoperative period has not been uniformly provided and whether this has been calculated when reporting total amounts of fluid administered is unclear. The impact of ODM-guided fluid administration on post-operative fluid management is hitherto unknown, though administration of supplementary colloid fluids in patients undergoing laparoscopic cholecystectomy showed greater postoperative urinary excretion.(331) Senagore standardised postoperative fluid management but administered a mean total of 19L of IVF during a patient’s hospital stay to patients receiving ODM-guided colloid based on physiological indications.(289) Future studies should also record postoperative fluid administration to ratify these seemingly large amounts.

The ODM algorithms were very similar between four of the trials and had the common aim of optimising cardiac indices as a proxy for tissue perfusion. However, it has been recently shown that ODM-guided stroke volume (SV) recordings must be
averaged over ten heartbeats to decrease measurement variability. (332) Without suitable calibration, inadequate estimates of SV can lead to inappropriate administration of fluid. (332) This has not been stated in the trials and may not have been possible with earlier models of instruments. The strategy for fluid administration across the control groups was also not well defined and may have caused substantial heterogeneity in the management of patients within this group.

Moreover, the trials used different colloid fluids which are different in molecular composition with variable vascular permeability and excretion parameters and hence remain in the intravascular compartment for differing lengths of time. (76, 130) The crystalloid carrier solutions of individual colloids contain varying quantities of chloride and in large volumes can cause hyperchloraemic acidosis which may have clinical significance. (76, 124) Future studies should also evaluate the role of newer balanced colloid solutions in this setting as done by Senagore. (127)

The patients in the trials by Gan and Senagore also received crystalloid bolus fluid based on ODM recordings though this is potentially inferior to colloid fluids (6% hydroxyethyl starch) in optimising the colonic microcirculation. (245) Very little information was specified generally on the type of fluids used in the control groups and only one trial reported a policy for administration of blood products. Blood transfusions represent a physiological colloid and hence the indications for their use within a trial exploring administration of colloid fluids should be standardised. (288)

The use of vasopressors was not sufficiently described in any of the trials as a part of the intraoperative management of the patient even though this has a significant impact on the patient’s cardiovascular function and can alter fluid requirements. (31) Whilst corrected flow time (FTc) is a preload index and has been validated as a predictor of fluid responsiveness, it has not been thoroughly evaluated
in the context of inotrope use in abdominal surgery.(333, 334) Similarly, intraoperative epidural analgesia was only utilised in one of the trials.(247) Epidural analgesia is utilised both intraoperatively and postoperatively during colonic surgery in many centres as it provides excellent analgesia and has been shown to decrease the duration of postoperative ileus and attenuate the post-surgical neuroendocrine response.(52) Importantly, however, ODM measurements overestimate cardiac output when epidural analgesia is used and may lead to inadequate fluid administration.(335)

The advent of laparoscopic colonic surgery and ERAS protocols has radically altered expectations of LOS and morbidity following colorectal surgery.(19, 72, 217, 270, 336) Some institutions have reported a median day-stay of two days following colonic resections with day-stay colectomy possible in highly selected patients.(23, 33, 337, 338) Four of the five trials were powered for hospital LOS but discharge criteria were not uniformly specified. Senagore defined LOS as “number of nights spent in-hospital” but reported day-stay results in hours and demonstrated a statistically significant difference in favour of standard fluid therapy.(289) However, the clinical significance between a LOS of 64.9 hours and 71.8 hours is questionable as this still represents three days. Moreover, since day-stay is usually a non-parametric measure and influenced by the presence of complications, medians are a more appropriate measure when reporting LOS.

LOS is affected by multiple factors and future trials should evaluate the impact of fluid management on available measures of recovery after surgery.(339, 340) Moreover, the reported LOS in both the control and intervention arms of each trial are considerably longer than reported LOS data from published ERAS protocols around the world.(338) This is partially due to the ODM trials utilising non-optimised
perioperative care. Only the most recently published trial by Senagore is an exception to this.(289) As an example, three of the trials report use of mechanical bowel preparation which is not regularly utilised for colonic surgery now due to concerns regarding dehydration, electrolyte imbalance and deleterious effects on bowel anastomoses.(27) Similarly, when the timing of IDC removal is not specified or early postoperative mobilisation is not explicitly encouraged, it is difficult to assess the impact of ODM-guided fluid administration on urinary tract infections and respiratory complications respectively.(44, 341)

ODM-guided fluid administration has also not been duly investigated in the setting of laparoscopic colonic resections with the haemodynamic changes that accompany pneumoperitoneum and necessary positional changes.(342-344) None of the trials were powered to detect a difference in complications. The meta-analyses which have found decreased complications in patients undergoing ODM-guided fluid administration may also have been influenced by trials evaluating non-fluid-related complications (e.g. Social complications).(244) This has reduced the generalisability of the published trials exploring ODM-guided intraoperative fluid administration.

The trial by Senagore has been published recently and its strengths include a selective patient population undergoing laparoscopic colectomy and optimised perioperative care. However, the primary objective of this trial appears to be a comparison of ODM-guided crystalloid and colloid administration and though LOS has been reported in an unconventional manner (in hours) and complications have not been defined, clearly it is cautionary to note that ODM-guided fluid administration has led to a longer LOS and significantly more complications.
It must be acknowledged that this study is reliant upon the published versions of the trials and as such, it is possible that certain methodological elements of the study were in fact conducted but not reported in the manuscript.

In conclusion, the published literature has demonstrated that ODM-guided fluid administration in colorectal surgery improves cardiac indices and tissue perfusion. However, procedure-specific evidence of clinical benefits is scarce and widespread use of ODM is based on small, single-centre trials. Moreover, the clinical benefits observed in published trials may be influenced by heterogeneous perioperative environment as was discussed in chapter two and potentially offset by the recent advances in perioperative care. Whether ODM-guided intraoperative fluid administration is superior to intraoperative fluid restriction and leads to clinically significant improvements in an otherwise optimised environment with patients that are largely either ASA 2 or 3, remains to be seen and should be explored with well-designed prospective studies. Chapter six and seven present two prospective studies which evaluate GDFT and address some of the questions raised in this systematic review.
6. Goal-Directed Fluid Therapy in major elective rectal surgery – A prospective study

6.1 Introduction

The previous systematic review has outlined the evidence pertaining to ODM-guided fluid therapy in the setting of colorectal surgery. One observation made is that some of the published studies are specific to colorectal surgery whilst others have been conducted in patients undergoing a variety of major abdominal surgical procedures. (247, 288, 289) Moreover, most of the colorectal-specific studies have not made a distinction between colon and rectal surgery even though these operations have been shown to be physiologically distinct from one another with different patterns of morbidity. (345-348) Moreover, rectal surgery is often accompanied by the additional metabolic burden of stoma creation and bowel preparation. This may also influence postoperative fluid requirements. (312)

One study which made this distinction and explored ODM-guided fluid therapy in colonic surgery alone showed adverse outcomes in patients randomised to the treatment arm. Another trial has also been published subsequent to the review in Chapter five and has also shown no benefits from GDFT with a trend towards inferior outcomes. (289, 290)

Important shortcomings of the evidence base governing GDFT in major colorectal surgery have led us and other authors to conclude that further procedure-specific studies are necessary. (312, 321) Thus, a prospective study was conducted to examine the influence of GDFT on clinical outcomes after elective rectal surgery.
6.2 Methods

6.2.1 Study design

Following regional and institutional ethical approval, informed consent was obtained from 27 consecutive patients undergoing major elective rectal surgery at our institution. These patients all received intraoperative GDFT as guided by ODM measurements and were compared to a historical cohort of the previous 54 patients for a total of 81 consecutive patients.

6.2.2 Inclusion and exclusion criteria

Rectal surgery was defined as any resection including a section of bowel within 15cm of the anal verge. Exclusion criteria for the study were acute operations, patient refusal, severe bleeding diathesis, severe oesophageal disease, recent oesophageal surgery and moderate/severe aortic valve disease as assessed by transthoracic echocardiogram.

6.2.3 Data points of interest

Baseline and demographic characteristics were noted. The primary outcome for the study was 30-day total complications and these were graded and defined based on published criteria. The secondary outcomes for the study were day to meet discharge criteria, hospital length of stay, administered fluid volumes in the preoperative, intraoperative and postoperative period and total intravenous fluid administered. The intraoperative period was defined as the time within which the patient was in the operating theatre with the preoperative and postoperative period being before and after respectively.

6.2.4 Data collection

Clinical outcomes for the treatment group were noted prospectively and at the conclusion of patient recruitment, all outcomes were verified by personnel blinded to
patient allocation on an intention-to-treat basis. If there was disagreement with prospective recording even after verification in person, the outcome was recorded as per the blinded person’s interpretation.

6.2.5 Preoperative management

The principles of enhanced recovery care were followed though a formal protocol has not been established for rectal surgery within our institution. Patients receiving bowel preparation were administered one litre of crystalloid fluid prior to surgery (Plasmalyte™, Baxter Healthcare, NSW, Australia). Use of bowel preparation was at the surgeon’s discretion.

6.2.6 Intraoperative management

All aspects of surgical technique were left up to the consultant surgeon.

All patients received volatile general anaesthesia and thoracic epidural analgesia was used, unless contraindicated, and activated from the initiation of the case. A low dose vasopressor infusion was used with metaraminol as the most common pressor. Patients received invasive blood pressure monitoring at the discretion of the anaesthetist.

All patients in the treatment group had continuous Oesophageal Doppler monitoring (Cardio Q, Pharmaco Inc, Auckland, NZ) and had a disposable oesophageal probe inserted for this purpose (DP-12, Pharmaco Inc, Auckland, NZ). Monitoring was discontinued at the end of the operation and the probe was removed prior to extubation in the operating room. The ODM probe was inserted and operated by a trained research assistant who had no input into any other aspects of perioperative care. All data were recorded over an average of ten cycles.(332) Intraoperative fluid administration was in conjunction with the anaesthetist and was
guided by a previously used protocol relying on obtained measurements of corrected flow time and stroke volume. (247, 288) Weight-based boluses of hydroxyethyl starch colloid (Voluven, Fresenius Kabi, NSW, Australia) were administered as outlined in the protocol. Further details pertaining to the technical aspects of the ODM are mentioned in the following chapter. Plasmalyte™ was used as the intraoperative crystalloid. Blood products were used if the haemoglobin was less than 80g/L in an otherwise well patient or less than 100g/L in a patient with documented cardiac disease. Patients in the control group were managed without the ODM and their fluid management was at the discretion of the anaesthetist. Further details regarding the ODM are as per chapter one and chapter seven.
Figure 7: Intraoperative fluid administration protocol

6.2.7 Postoperative care

The principles of enhanced recovery care were followed though a formal protocol has not been established for rectal surgery within our institution. Patients were
allowed to eat solid food from the evening of the operation. Oral fluid intake was also encouraged as well as early mobilisation. Caloric supplementation was also provided (Fortisip, Nutricia Inc, Auckland, New Zealand). Epidural analgesia was continued till 72 hours postoperatively and urinary catheters were left in till this time. Simple oral analgesia was provided regularly with avoidance of opioid analgesia unless required for break-through pain. Non-steroidal analgesia was used from postoperative day two (20mg Tenoxicam, Valeant Pharmaceuticals Ltd, Auckland, New Zealand).

All intravenous fluids were stopped upon the patient arriving at the ward and oral intake of food, fluids and supplements was encouraged. The patient was then formally assessed by the ward doctor to decide whether any intravenous fluid was necessary. Clinicians were required to see the patient and document their findings and were not allowed to make decisions over the phone. This judgement was based on patient observations, clinical examination and urine output. Examination findings consistent with volume deficit were required to prescribe intravenous fluid (e.g. decreased jugular venous pulse). Intravenous fluid was administered if patients were oliguric (defined as less than 0.5ml/kg/hr averaged over four hours) or had deranged physiological parameters suggestive of volume deficit (tachycardia (>90bpm), hypotension (systolic blood pressure < 90mmHg in the presence of a functioning epidural; <100mmHg without an epidural). Intravenous fluid was also administered for resuscitative purposes in the event of complications, to compensate for losses such as in high output stomae or for poor oral intake such as in paralytic ileus.

6.2.8 Discharge criteria

The following criteria had to be satisfied for patients to be eligible for discharge: Pain managed by oral analgesia alone; able to mobilise at least to and from the toilet; passage of flatus either per rectally or via stoma; able to tolerate solid foods;
satisfactory capability to manage stoma as determined by the stoma therapist; normalising blood tests including C reactive protein; absence of complications.

6.2.9 Statistical analysis

Based on internal audit data, using a two-tailed Fisher’s exact test in a 1:2 ratio, with an alpha of 0.05 and power of 80%, 27 patients were needed in the treatment group to detect a 30% difference in the primary outcome. Data were analysed using the Mann-Whitney U Test and the two-tailed Fisher’s exact test with \( p < 0.05 \) being considered statistically significant. SPSS v13.0 (SPSS Inc, Irv, CA) was used for all statistical analysis.

6.3 Results

6.3.1 Patient recruitment and demographics

All eligible patients consented to participate in the study and thus 27 consecutive patients were recruited and compared with the previous 54 patients. One patient in the treatment group became too unstable due to intraoperative haemorrhage and the protocol was abandoned in favour of a massive transfusion protocol as per hospital guidelines. There were no other violations of the protocol. The patients were well matched at baseline as shown in Table 23.
Table 23: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>GDFT (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median [range]</strong></td>
<td>63 [18–86]</td>
<td>61 [27–87]</td>
<td>0.89‡</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>17 (63%)</td>
<td>24 (44%)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>BMI, mean (SD)</strong></td>
<td>27.1 (5.5)</td>
<td>27.8 (6.6)</td>
<td>0.73§</td>
</tr>
<tr>
<td><strong>Preoperative haemoglobin, mean (SD)</strong></td>
<td>130 (17)</td>
<td>127 (19)</td>
<td>0.53†</td>
</tr>
<tr>
<td><strong>ASA score, median [range]</strong></td>
<td>2 [1–3]</td>
<td>2 [1–3]</td>
<td>0.66‡</td>
</tr>
<tr>
<td><strong>Cr-POSSUM, median [range]</strong></td>
<td>9 [6–18]</td>
<td>10 [6–21]</td>
<td>0.74‡</td>
</tr>
<tr>
<td><strong>Operation severity, median [range]</strong></td>
<td>7 [7–12]</td>
<td>7 [7–13]</td>
<td>0.85‡</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>25 (93%)</td>
<td>46 (85%)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Dukes stage</strong></td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>4 (15%)</td>
<td>9 (17%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>9 (33%)</td>
<td>10 (19%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>11 (41%)</td>
<td>24 (44%)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>1 (4%)</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Operation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior resection</td>
<td>11 (41%)</td>
<td>29 (54%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Abdominoperineal resection</td>
<td>11 (41%)</td>
<td>17 (31%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Other</td>
<td>5 (19%)</td>
<td>8 (15%)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Surgical technique</strong></td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Open</td>
<td>27 (100%)</td>
<td>49 (91%)</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>0 (0%)</td>
<td>5 (9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stoma</strong></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>26 (96%)</td>
<td>52 (96%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Operation time, mean (SD)</strong></td>
<td>196 (56)</td>
<td>206 (65)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Arterial line</strong></td>
<td>18 (67%)</td>
<td>30 (56%)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Epidural</strong></td>
<td>19 (70%)</td>
<td>45 (83%)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesiologists; BMI: Body Mass Index (kg/m²); Cr-POSSUM: Colorectal Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; SD: standard deviation. Fisher’s exact test used unless otherwise stated; ‡ Mann-Whitney U test; † t test

6.3.2 Clinical outcomes

Administered fluid amounts are shown in Table 24. Patients in the treatment arm received more colloid fluids intraoperatively though there was no difference in total fluid volumes administered intraoperatively. There were no other statistically significant differences between administered fluid volumes in the perioperative period. There was a non-significant trend showing a decreased fluid requirement for the first 24 hours postoperatively in patients receiving GDFT (p=0.06).
Table 24: Perioperative fluid amounts

<table>
<thead>
<tr>
<th></th>
<th>GDFT (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid</td>
<td>1000 [0–1000]</td>
<td>875 [0–2220]</td>
<td>0.61</td>
</tr>
<tr>
<td>Colloid</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Intraoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid</td>
<td>2000 [300–4200]</td>
<td>3000 [1000–6000]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Colloid</td>
<td>1000 [0–2500]</td>
<td>500 [0–1500]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total fluid</td>
<td>3000 [1000–6500]</td>
<td>3000 [1500–6000]</td>
<td>0.41</td>
</tr>
<tr>
<td>Blood transfusion†</td>
<td>7 (26%)</td>
<td>6 (11%)</td>
<td>0.11‡</td>
</tr>
<tr>
<td>Inotrope†</td>
<td>22 (82%)</td>
<td>51 (94%)</td>
<td>0.11‡</td>
</tr>
<tr>
<td><strong>Postoperative Day 0</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid</td>
<td>1000 [0–6500]</td>
<td>1025 [0–4200]</td>
<td>0.54</td>
</tr>
<tr>
<td>Colloid</td>
<td>0 [0–1000]</td>
<td>0 [0–1500]</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Postoperative Day 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid</td>
<td>1450 [0–4630]</td>
<td>1780 [0–4250]</td>
<td>0.06</td>
</tr>
<tr>
<td>Colloid</td>
<td>0 [0–1250]</td>
<td>0 [0–1250]</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Postoperative Day 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid</td>
<td>500 [0–4920]</td>
<td>1000 [0–4550]</td>
<td>0.28</td>
</tr>
<tr>
<td>Colloid</td>
<td>0 [0–500]</td>
<td>0 [0–1500]</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Postoperative Day 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid</td>
<td>0 [0–5760]</td>
<td>295 [0–6600]</td>
<td>0.87</td>
</tr>
<tr>
<td>Colloid</td>
<td>0 [0–750]</td>
<td>0 [0–3000]</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Total postoperative fluid Day 1–3</strong></td>
<td>3800 [0–15816]</td>
<td>5500 [1000–13640]</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Total postoperative fluid</strong></td>
<td>7840 [0–61350]</td>
<td>6605 [1000–38160]</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Total fluid</strong></td>
<td>12700 [2600–63550]</td>
<td>10407 [5000–43660]</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Fluid amounts are shown in millilitres and expressed as medians [range]. †: Expressed as number of patients receiving blood transfusion or inotropes. Mann-Whitney U test used unless otherwise stated. ‡: Fisher’s exact test.

There were no differences in clinical outcomes between the two groups as shown in Table 25.
Table 25: Postoperative complications and hospital stay

<table>
<thead>
<tr>
<th>Complication</th>
<th>GDF (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>22 (81%)</td>
<td>44 (81%)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>5 (19%)</td>
<td>10 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complication grade</th>
<th>GDF (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2 (7%)</td>
<td>4 (7%)</td>
<td>1.00</td>
</tr>
<tr>
<td>II</td>
<td>15 (56%)</td>
<td>26 (48%)</td>
<td>0.64</td>
</tr>
<tr>
<td>III</td>
<td>1 (4%)</td>
<td>4 (7%)</td>
<td>0.66</td>
</tr>
<tr>
<td>IV</td>
<td>4 (15%)</td>
<td>2 (4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>V</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complication type</th>
<th>GDF (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiorespiratory</td>
<td>7 (26%)</td>
<td>9 (17%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Abdominal collection</td>
<td>4 (15%)</td>
<td>3 (6%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1 (4%)</td>
<td>9 (17%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (7%)</td>
<td>8 (15%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Ileus</td>
<td>5 (19%)</td>
<td>6 (11%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>2 (7%)</td>
<td>2 (4%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (4%)</td>
<td>5 (9%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day of flatus</th>
<th>GDF (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [1–4]</td>
<td>1 [1–6]</td>
<td>0.90‡</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day to meet discharge criteria</th>
<th>GDF (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 [3–109]</td>
<td>8 [3–32]</td>
<td>0.98‡</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discharge day</th>
<th>GDF (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 [3–109]</td>
<td>9 [3–32]</td>
<td>0.52‡</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Readmissions</th>
<th>GDF (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (15%)</td>
<td>11 (20%)</td>
<td>0.76</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Total hospital stay</th>
<th>GDF (n=27)</th>
<th>Control (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 [3–109]</td>
<td>10 [3–33]</td>
<td>0.92‡</td>
<td></td>
</tr>
</tbody>
</table>

Discharge data and hospital stay are expressed as medians [range]. Fisher's exact test used unless otherwise stated. ‡: Mann-Whitney U test

6.4 Discussion

This prospective study has demonstrated that intraoperative GDF did not improve clinical outcomes in patients undergoing major elective rectal surgery. The administered fluid volumes between the two groups were not significantly different though patients allotted to GDF received a higher proportion of colloid intraoperatively. A non-significant trend suggested that patients in the treatment arm had decreased fluid requirements for the first 24 hours after surgery.
The findings of this study are dissimilar to previously published trials and meta-analyses that have been the basis for policy decisions. This may be due to this study being different from previous studies in several ways. The current study was conducted in rectal surgery alone. Rectal surgery has been shown to be physiologically distinct from colonic surgery as evidenced by patterns of cytokine release and also has different patterns of morbidity. It also requires a pelvic dissection along with colonic mobilisation intraoperatively. Moreover, rectal surgery is more likely to require preoperative bowel preparation and be accompanied by the creation of a stoma which poses an additional metabolic burden. Furthermore, stoma outputs can increase gastrointestinal losses and may affect postoperative fluid requirements especially in high output states. Therefore, the published positive findings in colonic resection and major abdominal surgery may not be able to be extrapolated to rectal surgery.

Some previous studies have not clarified their postoperative fluid management protocol. In patients undergoing rectal surgery, postoperative fluid administration may be higher compared to colonic surgery due to replacement fluid being required for high stoma outputs or greater awareness of oliguria due to the urinary catheter being in-situ for longer. These high volumes of postoperative fluid are not guided by intensive monitoring as in the intraoperative phase and may offset any potential gains from achieving fluid balance in the intraoperative period. This may be more relevant than in colonic surgery where patients receive less intravenous fluid postoperatively.

Our institution utilises an Enhanced Recovery protocol for patients undergoing elective colectomy. This study was also conducted in an environment of current perioperative practices such as early feeding, use of epidural analgesia and
preoperative carbohydrate loading. Whilst these elements were not formally implemented as for the colectomy patients, the results are potentially more applicable to current practice compared to previous trials which were conducted in the setting of non-optimised perioperative care. As shown in Chapter two, the perioperative environment can greatly influence fluid administration. It is also important to note that other studies exploring GDFT within an established enhanced recovery environment have shown equivalent or inferior outcomes for patients receiving GDFT and perhaps the previously demonstrated benefits of GDFT have been offset by improvements in other aspects of perioperative care.(289, 290)

Moreover, the volume of fluid administered in the control arm in this study could be regarded as ‘restrictive’ or ‘balanced’ by some definitions(43) and no definite superiority between restrictive and GDFT regimens has been demonstrated to date.(312)

This study suffers from the limitation of not having a defined protocol for fluid management in the control arm as in previous studies. Whilst it has been recognised that commonly available monitoring indices (heart rate, intraoperative urine output, blood pressure, cyclic arterial pressure variations) are not sensitive markers of fluid responsiveness, the exact basis of decision making concerning fluid administration by individual anaesthetists in this study or others is unlikely to be as simplistic as a rigid protocol. Since this was a non-randomised study, the possibility of confounders cannot be definitively ruled out. However, the study was conducted in a short time frame decreasing the likelihood of other changes in management. The baseline characteristics were also noted and shown to be equal. Even the prospective group of patients had complications ratified by review of notes by blinded personnel and thus there was equivalent rigour in the recording of complications in both groups. A weakness of the study due to this design was, however, that urine output, weights
and cardiac output were not noted since it was known that these data would not be available for the control group, thus preventing any comparison.

In the post-operative setting, 0.5ml/kg/hr was used as the benchmark of adequate urine output. Although permissive oliguria has been proposed in other settings, this number was chosen on the basis of historical precedence and because hospital guidelines and nursing observations and thresholds to seek review are based upon this parameter. Fluid administration was rationalised as four-hour averages were sought in otherwise well patients.

This study had a seemingly high complication rate. However, this is the likely consequence of meticulous recording as the bulk of the complications were grade one and two in severity. Even though cardiovascular complications seem high, very few of these were actually significant. E.g. Patients with high output stomata were prescribed loperamide and intravenous fluid. If no renal impairment resulted, these were coded as cardiovascular. This also resulted in inflation of the cardiovascular complication rate.

This study also showed a non-significant trend suggesting that patients managed with GDFHT had decreased fluid requirements in the first 24 hours after surgery. The absolute volumes of fluid administered remained lower in the GDFHT group for three days postoperatively but these findings were less statistically compelling. A potential reason for this is that even though administered intraoperative fluid amounts were the same, a greater amount of colloid fluid in the treatment group may have lead to greater intravascular volume replacement. It is therefore important to acknowledge that patients in the GDFHT group received more intravascular fluid but any potential improvement in circulatory support did not translate into improved clinical outcomes.
It is important to note that this study is not a randomised trial. Despite the limitations surrounding the evidence concerning GDFT, it is still supported by a number of randomised trials. Large phase four studies have also shown improvements in clinical outcomes with the use of GDFT. (300) Importantly, however, this study is the only one to be powered specifically for total complications in rectal surgery and has not shown any clinical benefits within a setting of contemporary perioperative care. These results cannot be extrapolated to colonic surgery for the reasons mentioned above and it is not known whether the lack of benefit demonstrated is specific to rectal surgery or a consequence of the other aspects of perioperative care, which may similarly influence outcomes of GDFT in colonic resection. Chapter seven looks to further address this question through the conduct of a randomised trial in patients undergoing elective colectomy.
7. Randomised trial of Goal-Directed Fluid Therapy versus intraoperative fluid restriction in elective colectomy within an ERAS protocol

7.1 Introduction

This thesis has explored perioperative fluid therapy within the context of optimised perioperative care. It has shown that intraoperative fluid management is a contentious issue as liberal fluid administration has been discarded by many practitioners in favour of restrictive or GDFT regimens. (187, 319) Previous trials have shown that restrictive fluid regimens decrease morbidity and accelerate recovery. (43, 111, 215) Similarly, other trials have shown that patients randomised to receive GDFT experience fewer complications and have shorter hospital length of stay, when compared to patients receiving liberal fluid therapy. (243, 244, 247, 288) Subsequent meta-analyses of the two competing strategies have shown each to be beneficial when compared to traditional, liberal fluid regimens. (72)

There are therefore two fluid administration strategies which have been proposed to be optimal without any direct comparison to each other. However, these strategies are contradictory to an extent since patients in some of the trials investigating GDFT have received greater volumes of fluids than patients randomised to restrictive fluid regimens in other trials. Moreover, the majority of these trials have been conducted in heterogeneous, non-optimised perioperative care settings, which may influence fluid administration as shown in chapter two. Any benefits observed may be offset by the advances in other aspects of perioperative care over the intervening period. (46, 312) There are also other important questions which remain unanswered regarding both restrictive and goal-directed fluid regimens. (223, 312) Previous authors have thus called for procedure-specific randomised trials to be conducted within an
otherwise homogeneous environment. (46, 322) Chapter five and six have also demonstrated the necessity of updated studies, whilst chapter four demonstrated that clinical equipoise remains, which may facilitate the conduct of a prospective study. Therefore, we conducted a randomised trial comparing GDFT with intraoperative fluid restriction in patients undergoing elective colectomy within an established ERAS protocol.

7.2 Methods

7.2.1 Study design

This was a prospective, double-blinded, single-centre randomised controlled trial with a 1:1 patient allocation ratio.

7.2.2 Participants

Consecutive consenting patients undergoing elective open or laparoscopic colectomy for any indication within our institution (Manukau Surgical Centre, Auckland, New Zealand) were enrolled into the trial. The exclusion criteria were as follows: severe oesophageal disease; recent oesophageal or upper airway surgery; moderate or severe aortic valve disease as proven by echocardiogram; documented bleeding diathesis; steroid dependency; cognitive impairment; ASA 4 or 5; rectal tumour (defined as less than 15cm from the anal verge); creation of a stoma and patient choice.

7.2.3 Interventions

The intervention was implemented in the intraoperative phase, which was defined as within the operating theatre. Any time prior to this was defined as the preoperative period and any subsequent period (including in the post-anaesthetic care unit) was
defined as the postoperative phase. Patients who received bowel preparation received one litre of preoperative crystalloid (Plasmalyte 148™).

Patients randomised to the fluid restriction arm were allowed to receive up to 1500mL of crystalloid solution (Plasma-Lyte 148, Baxter Healthcare, NSW, Australia) intraoperatively. They were also permitted to receive a further 500mL of succinylated gelatine colloid solution (Gelofusine, Braun Inc., NSW, Australia) as titrated by intraoperative heart rate, blood pressure, urine output and invasive measures from arterial lines when available. In the fluid restriction arm, any blood loss was allowed to be corrected in a 1:1 ratio using Gelofusine and hospital transfusion guidelines were used to determine if blood products were necessary in either arm. Patients randomised to the ODM-guided fluid therapy arm were also treated with baseline fluid restriction and received up to 1500mL of crystalloid solution. They also received weight-based boluses of Gelofusine based on measurements of cardiac function obtained from the ODM (CardioQ Oesophageal Doppler Monitor, Pharmaco NZ Ltd, Auckland, New Zealand). The machine was calibrated to provide data averaged over ten cycles. (332) The algorithm for fluid administration based on ODM-measurements is as per Figure eight and has been previously used in other studies. (247, 288) An extra 500mL of Plasmalyte 148 was allowed for every hour if the operation extended beyond three hours in both arms. Vasopressors and inotropes were permitted as per the anaesthetist’s discretion.
Figure 8: Fluid administration algorithm

**EVERY 15 MINUTES**

Ensure satisfactory probe position

Monitor FTc and SV

FTc < 350 ms

Yes

No

Monitor FTc and SV

Colloid (Gelofusin) Challenge

- 7 ml/kg first bolus (if low FTc)
- 3 ml/kg subsequent bolus (or initial SV)

Yes

FTc < 350 ms

No

FTc > 400 ms

Yes

Monitor FTc and SV

No

SV increased > 10% since previous bolus or measurement

FTc < 350 ms or SV decreased > 10%
7.2.4 Oesophageal Doppler Monitor

7.2.4.1 Equipment

The equipment consisted of a monitor and a disposable oesophageal probe. The monitor was fitted with a specially designed plastic casing (Acryform Ltd, Auckland, New Zealand) to assist with blinding (see Figure 9). The tip of the probe emits continuous wave ultrasound and also receives the reflected wave from the moving blood.

Figure 9: Oesophageal Doppler Monitor Cover

7.2.4.2 Principle

The ODM works upon the Doppler principle which has been shown to be a reliable method to measure blood flow and related haemodynamic variables. The density difference between red blood cells and surrounding plasma acts as an ‘acoustic impedance mirror’ and reflects incoming ultrasound waves. The probe thus measures blood velocity in the descending aorta over consecutive cardiac cycles to plot a curve or descending aortic blood velocity over time. The area under
this curve is calculated to measure stroke distance. Measurements of stroke distance are then converted to stroke volume using a validated nomogram incorporating patient specific variables of age, height and weight.(267) This nomogram was developed via correlating ODM-derived variables to PAC-derived values and has been shown to be both reliable and valid.(266, 267, 334) The ODM also measures heart rate and thus can calculate cardiac output \((CO=SV \times HR)\). Using patient-specific variables, the ODM can calculate cardiac index.

The ODM also displays the corrected flow time \((FTc)\), which is a measure of systolic ejection time corrected for heart rate using Bazett's equation.(351) \(FTc\) is inversely proportional to systemic vascular resistance and is an accurate measure to indicate changes in preload.

### 7.2.4.3 Operation of ODM

A disposable probe was connected to the ODM monitor, which was plugged in to an external power source and switched on. This prompts the user to enter in patient details of age, height and weight. The probe was lubricated and inserted in the oesophagus of sedated patients via either the oral or nasal cavity. The depth of insertion was between 40–45 cm from the incisors or nasal septum depending on the route of insertion and patient size. The probes were inserted by the same individual during the study who was beyond their learning curve.(327) The position of the probe within the oesophagus was manually adjusted until waveforms measuring blood flow in the descending aorta were visible and the characteristic sound of blood flow was heard. Once a suitable waveform was found, the volume was switched off unless further calibration became necessary. The typical appearance of these waveforms is as per Figure 10. The visual quality of the waveforms was further
optimised using automatic calibration through the ODM monitor and all data were
recorded over an average of ten cycles.(332)

Figure 10: Typical Oesophageal Doppler Waveform

7.2.4.4 ODM-guided fluid administration

Any change in cardiac output will be reflected by changes in descending aortic
blood flow. As a result, any change in cardiac output is reflected in numerical
measurements obtained by the ODM as well as the waveform appearance. The
theory behind ODM-guided fluid administration is to repeatedly administer weight-
based boluses of intravenous fluids at 15 minute intervals to optimise cardiac output
until the measurable cardiac indices do not significantly increase as a result of the
patient approaching the plateau phase of the Starling curve as shown in Figure 2.
The fluid administration algorithm is as per Figure 8 and uses the indices of FTc and SV.

7.2.5 Postoperative fluid administration

All intravenous fluids were stopped by default by nurses when patients arrived on the ward, typically one to three hours after surgery and oral intake of food, fluids and supplements was encouraged. The patient was then formally assessed by the ward doctor to decide whether any intravenous fluid was necessary. Clinicians were required to see the patient and document their findings and were not allowed to make decisions over the phone. This judgement was based on patient observations, clinical examination and urine output. Examination findings consistent with volume deficit were required to prescribe intravenous fluid (e.g. decreased jugular venous pulse). Intravenous fluid was administered if patients were oliguric (defined as less than 0.5ml/kg/hr averaged over four hours) or had deranged physiological parameters suggestive of volume deficit (tachycardia (>90bpm), low blood pressure (systolic blood pressure < 90mmHg in the presence of a functioning epidural; <100mmHg without an epidural) Intravenous fluid was also administered for resuscitative purposes in the event of complications, to compensate for losses or for prolonged poor oral intake such as in paralytic ileus. The only colloid used postoperatively was Gelofusine. Plasma-Lyte 148 was used postoperatively in the high dependency unit (HDU) and Dextrose-Saline solution (Dex Saline, Baxter Healthcare, NSW, Australia) (0.18% sodium chloride, 4% glucose, 20mmol/L potassium) was used as maintenance crystalloid on the ward when required.

7.2.6 Perioperative care

All patients were managed within an established ERAS protocol as described in chapter three.
7.2.7 Measurement of outcomes

All data outside the intraoperative phase were collected by a single, blinded investigator.

7.2.8 Primary outcome

The primary outcome of the study was the Surgical Recovery Score (SRS) on postoperative day (POD) seven. This endpoint was also measured preoperatively, on POD one, three, 14, 30.

7.2.8.1 Surgical Recovery Score (SRS)

The SRS is based upon the validated Identity-Consequence Fatigue Scale, which is a measure of postoperative recovery. (6, 339) The latter has been previously validated and used in patients undergoing colorectal surgery and shown to correlate to pro-inflammatory cytokine release. (6, 352) It is a 31-item questionnaire consisting of five components: feelings of fatigue; feelings of vigour; impacts on concentration; activities of daily living; impacts on energy levels. Each question is answered using a Likert scale with the option to ignore irrelevant questions (e.g. frequency of household chores when patient is an inpatient). Scores range from 17–100 with higher scores indicating better functional recovery and decreased post-surgical fatigue. It has been used in previous studies within our institution (38, 62), is validated and has been shown to correlate with the development of complications (Manuscript under review). A copy of the questionnaire is included in Appendix 1.

7.2.9 Secondary outcomes

7.2.9.1 Postoperative recovery

Grip strength was measured preoperatively and daily until postoperative day three using a hand held dynamometer (Hydraulic Hand Dynamometer; Jamar Inc., Chicago, IL, USA). The handle was adjusted for individual patients and the peak-
hold needle was calibrated to zero before every attempt. Patients were asked to sit either in bed or a chair with elbows flexed and supported. Forearm and wrist were maintained in a neutral position. Patients were instructed to use their dominant hand and were allowed a maximum of three tries with the average result recorded in kg/N.

Peak flow was measured preoperatively and daily until postoperative day three using a mini peak-flowmeter (Mini Wright Peak Flowmeter, Clement Clark Int. Inc, Essex, UK) attached to disposable mouthpieces. Patients were instructed to be seated, inhale and then exhale forcefully. All measurements were obtained in the seated position and patients were allowed to have three attempts with the best score recorded in L/min.

Thirty-day complications were prospectively recorded and were defined and graded as per the published criteria of Buzby and the Clavien-Dindo classification respectively.(314-316) Hospital length of stay during the index admission was recorded.

Patients were weighed preoperatively and daily until postoperative day three using an electronic weighing scale (Salter Inc, Auckland, New Zealand).

7.2.9.2 Fluid-specific data

Intraoperative cardiac indices (CI, FTc, HR) were obtained from the ODM at 15 minute intervals for both groups. Administered fluid volumes and vasopressor use were also recorded.

7.2.10 Laboratory indices

Preoperative and POD 1 serum brain natriuretic peptide (BNP), renin and aldosterone were measured. Serum electrolytes were measured preoperatively and daily until POD 3.
7.2.11 Cytokine analysis

Serum cytokines (IL-6, IL-8, TNF-α, IL-10, IL-1) were measured on POD one.

7.2.11.1 Use/ Purpose

A five-plex assay kit manufactured by Millipore Research was used for the quantitative determination of human cytokines. The cytokines to be measured were IL-1, IL-6, IL-8, IL-10, IL-13, TNF-α in plasma.

7.2.11.2 Contents

Reagents

- Antibody-immobilised beads
- #01-Human IL-1b
- #12-Human IL-6
- #20-Human IL-8
- #23-Human IL-10
- #26-Human IL-13
- #40-Human TNF-α
- Human Cytokine/ Chemokine standard cocktail 1 vial containing human cytokine standard cocktail, lyophilised quantity: 1 vial
- Human cytokine/ chemokine quality controls control I-1 vial containing mixed cytokine cocktail, lyophilized Control II- 1 vial containing mixed cytokine cocktail, lyophilised Quantity: 1 vial/ control
- Serum matrix, lyophilised. Serum containing 0.08% Sodium Azide Quantity: 1mL/vial
- Bead diluent 1 vial containing diluent for bead preparation Quantity: 3.5mL/bottle
- Mixing bottle quantity: 1 bottle
- Human cytokine/ chemokine detection antibodies 1 bottle containing a cocktail of biotinylated detection antibodies in Assay Buffer Quantity: 3.2mL/bottle
- Streptavidin-Phycoerythrin 1 bottle containing Streptavidin-Phycoerythrin prepared in Assay Buffer Quantity: 3.2mL/bottle
- Assay Buffer 50mM PBS with 25mM EDTA, 0.08% Sodium Azide, 0.05% Tween-20, and 1%BSA, pH 7.4. Quantity 30mL/bottle
• 10X Wash Buffer 1: 10 dilution required with deionised water to give 10mM PBS with 0.05% Proclin, and 0.05% Tween-20, pH 7.4. Quantity 30mL/bottle
• Microtiter Filter Plate: Quantity: 1-96 Well Filtration Plate
• Plate Sealers Quantity: 2 Plate Sealers

7.2.11.3 Storage conditions

The recommended storage for kit conditions were 2-8°C. Once the standards and controls were reconstituted, they were immediately transferred into polypropylene vials. For long term storage, reconstituted standards and controls were frozen at <-21°C. Multiple freeze thaw cycles were avoided.

7.2.11.4 Other materials used

Reagents
• Luminex Sheath fluid (Luminex Catalogue #40-50000)

Instrumentation/Materials
• Adjustable pipettes with tips capable of delivering 25-1000µL
• Multichannel pipettes capable of delivering 5-50µL or 25 -200µL
• Reagent reservoirs
• Polypropylene Microfuge Tubes
• Aluminium Foil
• Absorbent Pads
• Laboratory vortex mixer
• Sonicator (Branson Ultrasonic Cleaner, Model #B200)
• Titer Plate Shaker (Lab-Line Instruments, Model #4625)
• Vacuum Filtration Unit (Millipore Vacuum Manifold Catalogue #MAVM0960R)
• Luminex Instrument

7.2.11.5 Specimen Collection and Storage

A maximum of 25µL per well of serum or plasma was used
7.2.11.6 Preparation of Plasma samples

Plasma was collected using EDTA as an anticoagulant. The collected samples were transferred to the Middlemore hospital lab on crushed ice immediately following collection. The samples were centrifuged for 10 minutes at 1000Xg within 60 minutes of blood collection. Plasma was removed and assayed immediately. The samples were centrifuged again prior to assay setup on the day of the assay. Serum Matrix was used as the diluent for samples which required dilution prior to assay.

7.2.11.7 Technical guidelines

The Antibody-Immobilised beads were light sensitive and were covered with aluminium foil at all times. The assay plate containing beads were covered with aluminium foil during all incubation steps.

All reagents were allowed to warm to room temperature (20–25°C) before use in the assay.

The bottom of the Microtiter Filter Plate was prevented from coming into direct contact with any absorbent material during assay set-up or during incubation.

The bottom of the Microtiter Filter Plate was always dried and cleaned to prevent any leakage due to capillary action. All washing was only performed with the wash buffer provided.

The vacuum suction on the plate was kept as low as possible. It was recommended to use a vacuum setting that would remove 200μL of buffer in more than 5 seconds.

After hydration, all controls and standards were transferred to polypropylene tubes.
During the preparation of the standard curve, different pipette tips were used between each dilution and solutions were mixed well.

The standards prepared by serial dilution were used within one hour of preparation and all unused standards were discarded.

The plates were read immediately after the assay was finished.

The titre plate shaker was set at a speed which provided maximum agitation without splashing of liquid outside the wells (approximately 500–800rpm).

The needle probe was cleaned using Alcohol Flushes. Probe height was adjusted to the filter plate prior to reading an assay.

Serum matrix was used.

All reagents were vortexed well before they were added to the plate.

7.2.11.8 Preparation of Antibody-immobilised beads

Premixed beads were used and the antibody-bead bottle was sonicated for 30 seconds and then vortexed for one minute. 70µL from each antibody bead bottle was added to the Mixing Bottle and Bead diluents was added to bring the final volume to 3.0mL.

7.2.11.9 Preparation of Controls

Human cytokine Control 1 and Human cytokine Control 2 were first reconstituted with 250µL of deionised water, inverted several times to mix and then vortexed. The solution was allowed to set for 5–10 minutes. The controls were then transferred to appropriately labelled polypropylene microfuge tubes.
7.2.11.10 Preparation of Wash Buffer

The 10X wash buffer was brought to room temperature and mixed, thereby bringing all salts into solution. 30mL of 10X wash buffer was diluted with 270mL of deionised water.

7.2.11.11 Preparation of serum matrix

1.0mL of deionised water was added to the bottle containing lyophilised Serum matrix. The solutions were mixed well and allowed at least 10 minutes for complete reconstitution.

7.2.11.12 Preparation of Cytokine Standard

The Human Cytokine Standard Cocktails were reconstituted with 250µL of Deionised water to give a 10,000 pg/mL concentration of standard for all analytes. The vials were inserted several times and vortexed for ten seconds to ensure mixing. The vials were allowed to set for 5–10 minutes and then transferred to an appropriately labelled polypropylene microfuge tube. This was used at the 10,000pg/mL standard.

7.2.11.13 Preparation of Working Standards

Five polypropylene microfuge tubes were labelled 2000, 400, 80, 16 and 3.2pg/mL. 200µL of Assay buffer was added to each of the five tubes. Serial dilutions were prepared according to the following instructions: 50µL of the 10,000pg/mL reconstituted standard was added to the 2000pg/mL tube and was mixed well; 50 µL of the 2000 standard was added to the 400pg/mL tube and mixed well; 50 µL of the 400 standard was added to the 80pg/mL tube and mixed well; 50 µL of the 80 standard was added to the 16pg/mL tube and mixed well; 50 µL of the 16 standard
was added to the 3.2pg/mL tube and mixed well. The 0pg/mL standard (Background) was the assay buffer.

**Table 26: Preparation of Human Cytokine Standard**

<table>
<thead>
<tr>
<th>Standard concentration (pg/ml)</th>
<th>Volume of deionised water to add</th>
<th>Volume of standard to add</th>
</tr>
</thead>
<tbody>
<tr>
<td>10,000</td>
<td>250µL</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 27: Preparation of Working Standards**

<table>
<thead>
<tr>
<th>Standard concentration (pg/mL)</th>
<th>Volume of Assay Buffer to add</th>
<th>Volume of Standard to Add</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>200µL</td>
<td>50µL of 10,000pg/mL</td>
</tr>
<tr>
<td>400</td>
<td>200µL</td>
<td>50µL of 2000pg/mL</td>
</tr>
<tr>
<td>80</td>
<td>200µL</td>
<td>50µL of 400pg/mL</td>
</tr>
<tr>
<td>16</td>
<td>200µL</td>
<td>50µL of 80pg/mL</td>
</tr>
<tr>
<td>3.2</td>
<td>200µL</td>
<td>50µL of 3.2g/mL</td>
</tr>
</tbody>
</table>

7.2.11.14 Immunoassay procedure

The following precautions were taken during the immunoassay procedure:

All reagents were allowed to warm to room temperature (20–25°C) before use in the assay.

Placement of standards, 0 (Background) 3.2, 16, 80, 400, 2000, 10000 pg/mL, Controls 1 and 2, and samples were diagrammed on a Well Map Worksheet in a vertical configuration. All assays were run in duplicate.

The filter plate was put on a plate holder at all times during reagent dispensing and incubation steps and the bottom of the plate was ensured not to touch any surface.

The filter plate was blocked by pipetting 200µL of Assay Buffer into each well of the microtiter plate. The plate was then sealed and mixed on a plate shaker for ten minutes at room temperature (20–25°C).
The assay buffer was removed by vacuum. Any excess Assay Buffer was removed from the bottom of the plates by blotting on paper towels.

- 25µL of Assay buffer was added to the 0 standard (Background)
- 25µL of Assay buffer was added to the Sample wells.
- 25µL of each standard or control was added into the appropriate wells.
- 25µL of appropriate matrix diluent was added to the Background, Standards, and Control Wells. When assaying plasma, serum matrix was used.
- 25µL of Assay buffer was added to the appropriate wells.

The bead bottle was vortexed and 25µL of Mixed Beads were added to each well.

The plate was sealed and covered with aluminium foil, and incubated with agitation on a plate shaker overnight at 4°C.

The fluid was gently removed by Vacuum whilst avoiding inversion of plates.

The plates were washed 2 times with 200µL/well of Wash Buffer with wash buffer removal by vacuum filtration between each wash. Any excess Wash buffer was removed from the bottom of the plate by blotting on paper towels.

The Detection Antibody solution was allowed to warm to room temperature. 25µL of detection antibody cocktail was added into each well.

The samples was sealed and covered with aluminium foil and incubated with agitation on a plate shaker for one hour at room temperature (20–25°C).

25µL of Streptavidin-Phycoerythrin was added to each well containing the 25µL of Detection Antibody Cocktail.

The samples was sealed and covered with aluminium foil and incubated with agitation on a plate shaker for 30 minutes at room temperature (20–25°C).
All contents were gently removed by vacuum avoiding inversion.

The plate was washed twice with 200µL of/well of wash buffer, removing wash buffer by vacuum filtration between each wash. Any excess buffer on the bottom of the plate was wiped with a tissue.

150µL of sheath fluid was added to all wells. It was then covered with aluminium foil and the beads were re-suspended on a plate shaker for five minutes.

The plates were then run on the Luminex instrument.

The median data using 5 parameter or spline fit data reduction was saved and evaluated.

7.2.11.15 Equipment settings

The following settings were applied for the duration of the experiments:

- Events: 50 per bead
- Sample size: 50mL
- Bead set
  - 22 for IL-1
  - 36 for IL-6
  - 40 for IL-8
  - 44 for IL-10
  - 80 for TNF-α
- Gate (for 1.7 system): 8000 to 15,000

These specifications were for the Luminex100 with software v.1.7
7.2.11.16 Assay characteristics

Standard comparison

The following LINCOplex standards with known values of mass and standards were assayed together to provide the following conversion factor. These values were received from the National Institute of Biological Standards and Controls with assigned Bioassay units and approximate mass determinations.

Table 28: Standard comparison

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>NCI Lot #</th>
<th>1 milliplex pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>86/632</td>
<td>303 mIU/mL</td>
</tr>
<tr>
<td>IL-6</td>
<td>89/548</td>
<td>3.9 mIU/mL</td>
</tr>
<tr>
<td>IL-8</td>
<td>89/520</td>
<td>10.4 mIU/mL</td>
</tr>
<tr>
<td>IL-10</td>
<td>93/722</td>
<td>3.8 mIU/mL</td>
</tr>
<tr>
<td>TNF-α</td>
<td>88/786</td>
<td>154 mIU/mL</td>
</tr>
</tbody>
</table>

Assay Sensitivities (minimum detectable concentrations, pg/mL)

Table 29: Assay sensitivities

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Two-hour Assay Sensitivity</th>
<th>Overnight Assay Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>1.50</td>
<td>3.50</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.40</td>
<td>0.30</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.40</td>
<td>0.20</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.20</td>
<td>0.10</td>
</tr>
</tbody>
</table>

7.2.11.17 Precision

Intra-assay precision was generated from the mean of the %CV's from eight reportable results across two different concentrations of cytokines in a single assay. Inter-assay precision was generated from the mean of the %CV's from two reportable results across two different concentrations of cytokine across 8 different assays.
<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Intra-assay (%CV)</th>
<th>Inter-Assay (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>8.2</td>
<td>16.8</td>
</tr>
<tr>
<td>IL-6</td>
<td>8.1</td>
<td>11.6</td>
</tr>
<tr>
<td>IL-8</td>
<td>7.1</td>
<td>11.6</td>
</tr>
<tr>
<td>IL-10</td>
<td>5.2</td>
<td>9.5</td>
</tr>
<tr>
<td>TNF-α</td>
<td>10.5</td>
<td>15.9</td>
</tr>
</tbody>
</table>

Accuracy was defined as a percentage of cytokines recovered from samples spiked with a known quantity. It was generated from calculating the percentage of recovery of three different levels of cytokine spiked into five different human serum samples with known low or measurable cytokine levels.

Table 31: Accuracy of cytokine assay

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Percentage recovery in matrix</th>
<th>Percentage recovery in serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>118.9</td>
<td>105.2</td>
</tr>
<tr>
<td>IL-6</td>
<td>103.3</td>
<td>84.6</td>
</tr>
<tr>
<td>IL-8</td>
<td>108.3</td>
<td>100.5</td>
</tr>
<tr>
<td>IL-10</td>
<td>110.4</td>
<td>99.0</td>
</tr>
<tr>
<td>TNF-α</td>
<td>114.7</td>
<td>98.9</td>
</tr>
</tbody>
</table>

The results from cytokine analysis are reported in the appropriate section below.

7.2.12 Intraoperative protocol adherence

Adherence to the intraoperative fluid protocol was prospectively recorded.

7.2.13 Sample size

From previous data, ‘a priori’ power calculations indicated that to detect a 20% difference in the SRS with an α of 0.05 and β of 0.8 would require 37 patients in each arm.(38) Thus a sample size of 80 was decided upon. Due to a higher than anticipated number of exclusions, the sample size was increased to 85 patients after gaining consent from the ethics committee.
7.2.14 Randomisation
7.2.14.1 Sequence generation

Randomisation was conducted using random numbers obtained from an open source computer-based random number generator (http://www.random.org).

7.2.14.2 Allocation concealment

Allocation details were concealed in opaque envelopes and were only used on the day of surgery when patients were randomised.

7.2.14.3 Implementation

The randomisation sequence was generated by a third party not involved in the conduct of the study. Patients were recruited at the preadmission clinic and were consented in a private room with verbal explanations and the participant information sheets. Participants were free to withdraw consent at any time and all consent was verbally reaffirmed on the day of surgery. The allocation of patients to individual arms was performed by the research assistant intraoperatively after the insertion of the ODM probe prior to the beginning of surgery and prior to colloid administration.

7.2.15 Blinding

The patient, study investigators, surgeon and other medical staff responsible for patient care were blinded to patient allocation. All patients had the ODM probe (DP-12 probe, Cardio-Q, Deltex Healthcare, Auckland, NZ) inserted by a trained research assistant. The ODM monitor was covered by a custom-designed plastic casing (Acryform Inc, Auckland, New Zealand) to ensure blinding.

An unblinded research assistant and the consultant anaesthetist were aware of patient allocation. All fluid administration was protocol-driven and delivered by the unblinded-research assistant under the supervision of the anaesthetist. Suggested
action based on the ODM protocol was reconfirmed every 15 minutes between the research assistant and anaesthetist for patients in the GDFT arm. The research assistant was not involved in any postoperative data collection or perioperative care of the patients. The anaesthetist was prevented from looking at the readings obtained by the ODM for patients in the control group due to the plastic cover on the monitor. Intraoperative adherence to the fluid protocol was measured as mentioned previously.

A drape was placed to prevent the surgeons from observing fluid administration and the research assistant was instructed to attach intravenous fluids periodically for patients in the fluid restriction arm without actually administering them to mimic the anticipated practice of fluid boluses in the GDFT group.

7.2.16 Statistical analyses

The results were analysed using SPSS v17.0 (SPSS Inc., Chicago, IL, USA). Normality was assessed using the Kolmogorov-Smirnov test and visually using the Q-Q plot. Data have been reported as mean (standard deviation) and median (range) for parametric and non-parametric data respectively. The two-tailed Fisher’s exact test, Mann-Whitney U test and t test were used as appropriate. Repeated measures were analysed using the ANOVA test with Tukey’s correction. No subgroup analyses were planned and no post-hoc analyses were conducted. A p-value of less than 0.05 was considered as statistically significant and all data were analysed using intention to treat principles.

7.2.17 Ethics and trial registration

This study received both regional and institutional ethical approval prior to commencement and was prospectively registered at www.clinicaltrials.gov (US
National Library of Medicine, Bethesda, MD, USA). The trial identifier was NCT00911391.

7.3 Results

7.3.1 Participant recruitment and flow

This study was conducted from November 2009 to September 2011. Details regarding patient recruitment and subsequent analysis have been outlined within the CONSORT statement as per figure two. (353) Eleven patients were excluded following randomisation from the study due to the creation of an unplanned stoma intraoperatively. One patient in the fluid restriction arm had an unresectable transverse colonic lesion invading the pancreas and had a stoma created. One patient in the ODM-guided fluid therapy arm had a stapler misfire and a positive air leak test following the anastomosis. The staple line was oversewn and a defunctioning ileostomy was created. The other patients had stomas created as they were found to have rectal lesions intraoperatively (n=6) or a prolonged and difficult operative course with concern regarding poor vascularity of the bowel ends on clinical assessment (n=3). Stomas were not created due to intraoperative haemodynamic instability in any patient. Consistent measurements from the ODM were not available for one patient in the ODM-guided fluid therapy arm. Three patients (Two in the fluid restriction arm; One in the ODM-guided fluid therapy arm) had intraoperative protocol violations. The two patients in the fluid restriction arm received 500mL of extra crystalloid each and the patient in the ODM-guided fluid therapy arm received a 3ml/kg bolus of colloid when not indicated by the protocol. All patients were analysed on an intention to treat basis.
Figure 11: CONSORT 2010 Statement

Enrolment

Assessed for eligibility (n=98)

Excluded (n=13)
- Declined to participate (n=5)
- Investigators not available (n=5)
- Non-english speaking (n=1)
- Acute operation (n=1)
- Anaesthetist refusal (n=1)

Randomized (n=85)

Allocation

Allocated to GDFT (n=42)
- Received allocated intervention (n=37)
- Did not receive allocated intervention (Creation of stoma) (n=5)

Allocated to fluid restriction (n=43)
- Received allocated intervention (n=37)
- Did not receive allocated intervention (Creation of stoma) (n=6)

Follow-Up

Lost to follow-up (n=0)
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Discontinued intervention (n=0)

Analysis

Analysed (n=37)
- Excluded from analysis (n=0)

Analysed (n=37)
- Excluded from analysis (n=0)
7.3.2 Number analysed

A total of 74 patients were included in the final analysis (37 in each group). All patients had 100% follow-up for the primary outcome. All other measurements including all secondary variables measured during and beyond the index admission included data from over 90% of patients with the exception of serum BNP, which was measured in 64 out of 74 patients.

7.3.3 Baseline characteristics

Both groups were well matched at baseline as shown below

Table 32: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Fluid restriction (n=37)</th>
<th>GDFT (n=37)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72 (12)</td>
<td>69 (16)</td>
<td>0.26</td>
</tr>
<tr>
<td>Females: Males</td>
<td>15:22</td>
<td>18:19</td>
<td>0.48</td>
</tr>
<tr>
<td>ASA</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>0.52</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 (4.4)</td>
<td>26.9 (4.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Preop Haemoglobin (g/L)</td>
<td>125 (21)</td>
<td>118 (19)</td>
<td>0.17</td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemicolecotomy</td>
<td>17</td>
<td>14</td>
<td>0.64</td>
</tr>
<tr>
<td>Extended right Hemicolecotomy</td>
<td>5</td>
<td>4</td>
<td>1.00</td>
</tr>
<tr>
<td>High Anterior resection</td>
<td>14</td>
<td>14</td>
<td>1.00</td>
</tr>
<tr>
<td>Total/ Subtotal colectomy</td>
<td>1</td>
<td>5</td>
<td>0.20</td>
</tr>
<tr>
<td>Laparoscopic/HALS</td>
<td>6</td>
<td>5</td>
<td>1.00</td>
</tr>
<tr>
<td>Cr-Possum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiology</td>
<td>9 (6–15)</td>
<td>9 (6–16)</td>
<td>0.21</td>
</tr>
<tr>
<td>Operative severity</td>
<td>7 (7–12)</td>
<td>7 (7–13)</td>
<td>0.93</td>
</tr>
<tr>
<td>Malignancy</td>
<td>34</td>
<td>33</td>
<td>1.00</td>
</tr>
<tr>
<td>AJCC Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>3</td>
<td>1.00</td>
</tr>
<tr>
<td>II</td>
<td>15</td>
<td>14</td>
<td>1.00</td>
</tr>
<tr>
<td>III</td>
<td>12</td>
<td>10</td>
<td>0.80</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>21 (9)</td>
<td>24 (10)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

HALS: Hand-assisted laparoscopic surgery; BMI: Body mass index. Data presented as mean and standard deviation or median and range.
7.3.4 **Intraoperative parameters**

Data regarding intraoperative management of patients is as per Table 33. Intraoperative haemodynamic parameters are as per Table 324. Patients randomised to GDFT had higher intraoperative corrected flow time (FTc) with no differences observed in other variables including Cardiac Index.

<table>
<thead>
<tr>
<th>Table 33: Intraoperative parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OT time (M/SD)</strong></td>
</tr>
<tr>
<td>OT time (M/SD)</td>
</tr>
<tr>
<td>Pressor use</td>
</tr>
<tr>
<td>Epidural analgesia</td>
</tr>
<tr>
<td>Epidural successful</td>
</tr>
<tr>
<td>Arterial line</td>
</tr>
</tbody>
</table>

OT: Operating theatre

<table>
<thead>
<tr>
<th>Table 34: Intraoperative haemodynamic parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
</tr>
<tr>
<td>First measurement</td>
</tr>
<tr>
<td>Mean during case</td>
</tr>
<tr>
<td>Final measurement</td>
</tr>
<tr>
<td>Cardiac Index (L/min/m²)</td>
</tr>
<tr>
<td>First measurement</td>
</tr>
<tr>
<td>Mean during case</td>
</tr>
<tr>
<td>Final measurement</td>
</tr>
<tr>
<td>Corrected flow time (ms)</td>
</tr>
<tr>
<td>First measurement</td>
</tr>
</tbody>
</table>

7.3.5 **Fluid management**

Data regarding perioperative fluid management are as per Figure 3. Patients randomised to the ODM-guided fluid therapy arm of the study received significantly more colloid intraoperatively compared to the patients randomised to fluid restriction (Mean: 591 (471) mL vs. 297 (275) mL; p<0.01) and received an overall higher volume of intravenous fluid intraoperatively (Mean 1994 (590) mL vs. 1614 (420) mL;
No other statistically significant differences were seen between the two groups including no differences in the number of patients requiring blood transfusions (ODM: 13; Restriction: 12; \( p=1.00 \)). There were no differences between the groups with regards to daily weights, intraoperative or early postoperative (day zero) urine output as shown in Table 35. There were no differences between the groups with regards to serum electrolytes or vasoactive hormones as shown in Table 36.

**Figure 12:** Perioperative fluid volumes

![Perioperative fluid volumes](image)

**IVF:** Intravenous fluid. All data are presented as median and range

**Table 35:** Fluid related variables

<table>
<thead>
<tr>
<th></th>
<th>Fluid restriction</th>
<th>GDFT</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>76 (14)</td>
<td>76 (16)</td>
<td>0.88</td>
</tr>
<tr>
<td>Day 1</td>
<td>78 (14)</td>
<td>78 (16)</td>
<td>0.84</td>
</tr>
<tr>
<td>Day 2</td>
<td>78 (14)</td>
<td>78 (17)</td>
<td>0.88</td>
</tr>
<tr>
<td>Day 3</td>
<td>77 (13)</td>
<td>78 (17)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>D/c day</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative urine output (ml/kg/hr)</td>
<td>0.99 (0.54-2.90)</td>
<td>1.03 (0.47-4.29)</td>
<td>0.69</td>
</tr>
<tr>
<td>24 hour urine output (ml/kg/hr)</td>
<td>0.77 (0.31-1.81)</td>
<td>0.75 (0.31-2.30)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Data are presented as mean and standard deviation or median and range
Table 36: Serum electrolytes and vasoactive hormones

<table>
<thead>
<tr>
<th></th>
<th>Fluid restriction</th>
<th>GDFT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sodium (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>138 (3)</td>
<td>139 (3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Day 1</td>
<td>136 (3)</td>
<td>136 (3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Day 2</td>
<td>135 (4)</td>
<td>134 (4)</td>
<td>0.73</td>
</tr>
<tr>
<td>Day 3</td>
<td>135 (5)</td>
<td>135 (5)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Creatinine (µmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>79 (21)</td>
<td>76 (26)</td>
<td>0.50</td>
</tr>
<tr>
<td>Day 1</td>
<td>80 (21)</td>
<td>77 (23)</td>
<td>0.31</td>
</tr>
<tr>
<td>Day 2</td>
<td>76 (25)</td>
<td>78 (26)</td>
<td>0.81</td>
</tr>
<tr>
<td>Day 3</td>
<td>77 (27)</td>
<td>74 (30)</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Albumin (g/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>41 (3)</td>
<td>40 (4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Day 1</td>
<td>32 (5)</td>
<td>31 (4)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Brain Natriuretic Peptide (pmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>22 (3-217)</td>
<td>19 (5-112)</td>
<td>0.64</td>
</tr>
<tr>
<td>Day 1</td>
<td>50 (16-289)</td>
<td>49 (5-240)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Aldosterone/ renin ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>10 (12)</td>
<td>10 (10)</td>
<td>0.83</td>
</tr>
<tr>
<td>Day 1</td>
<td>8 (9)</td>
<td>9 (11)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

All data are presented as mean and standard deviation or median and range

7.3.6 Surgical recovery

There were no differences between the two groups at any point with regards to the primary outcome of surgical recovery as measured by the SRS (See Figure 13). There were no differences between the groups with regards to postoperative peak flow and grip strength as shown in Table 37.
Figure 13: Surgical recovery

All data are mean and standard deviation

Table 37: Grip strength and peak flow

<table>
<thead>
<tr>
<th></th>
<th>Fluid restriction</th>
<th>GDFT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>Grip Strength (kg/N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>31</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>Day 1</td>
<td>29</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Day 2</td>
<td>28</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>Day 3</td>
<td>27</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>Peak Flow (L/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>392</td>
<td>156</td>
<td>362</td>
</tr>
<tr>
<td>Day 1</td>
<td>238</td>
<td>113</td>
<td>215</td>
</tr>
<tr>
<td>Day 2</td>
<td>243</td>
<td>100</td>
<td>228</td>
</tr>
<tr>
<td>Day 3</td>
<td>235</td>
<td>103</td>
<td>230</td>
</tr>
</tbody>
</table>
7.3.7 Serum cytokine analysis

Table 38: Serum cytokine release on postoperative day one

<table>
<thead>
<tr>
<th>Fluid restriction</th>
<th>ODM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>IL-1α</td>
<td>3.2</td>
<td>0.3–37.2</td>
</tr>
<tr>
<td>IL-6</td>
<td>26.4</td>
<td>1.5–400.4</td>
</tr>
<tr>
<td>IL-8</td>
<td>16.3</td>
<td>2.8–123.0</td>
</tr>
<tr>
<td>IL-10</td>
<td>13.1</td>
<td>0.07–82.1</td>
</tr>
<tr>
<td>TNF-α</td>
<td>10.5</td>
<td>1.3–42.3</td>
</tr>
</tbody>
</table>

All measurements in pg/mL. Mann-Whitney Test used for all comparisons

7.3.8 Clinical outcomes

There were no differences between the two groups with regards to 30-day total complications (Fluid restriction: n=27, GDFT: n=26; p=1.00). No differences were found when complications were assessed by grade of severity or type including no difference with regards to the incidence of cardiopulmonary complications (5 vs. 5; p=1.00). No patients suffered renal impairment and there was no difference between groups with regards to hospital length of stay (Fluid restriction: 5 (2–49) vs. GDFT: 6 (3–41) days; p=0.57).

Table 39: Clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication (No of patients)</td>
<td>27</td>
<td>26</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Complication Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Fluid restriction</th>
<th>GDFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>V</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Major complications (III, IV, V)</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

Complication type

<table>
<thead>
<tr>
<th>Type</th>
<th>Fluid restriction</th>
<th>GDFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>15#</td>
<td>14^</td>
</tr>
</tbody>
</table>

160
<table>
<thead>
<tr>
<th>Other</th>
<th>12*</th>
<th>12~</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readmissions</td>
<td>4</td>
<td>9</td>
<td>0.22</td>
</tr>
<tr>
<td>Hospital Length of Stay</td>
<td>5 (2-49)</td>
<td>6 (3-41)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

#Intra-abdominal collection (n=0); Anastomotic leak (n=5); Wound infection (n=7); Ileus (n=3)

^ Intra-abdominal collection (n=2); Anastomotic leak (n=6); Wound infection (n=5); Ileus (n=1)

*Cardiorespiratory (n=5); Urinary (n=3); Haemorrhage (n=4); Renal impairment (n=0); Other (n=0)

~ Cardiorespiratory (n=5); Urinary (n=3); Haemorrhage (n=2); Renal impairment (n=0); Other (n=2)

7.4 Discussion

This randomised trial has shown that GDFT and intraoperative fluid restriction provided equivalent outcomes for patients undergoing elective colectomy within an ERAS protocol. Patients randomised to GDFT received more colloid intraoperatively with a consequent higher volume of intraoperative intravenous fluid and had superior aortic flow velocity. However, this did not translate into any differences between the two groups with regards to surgical recovery, physiological variables, serum electrolytes, vasoactive hormones or clinical outcomes.

Earlier trials investigating GDFT in the setting of major abdominal surgery have shown clinical benefits when compared to traditional, liberal fluid therapy.(243, 244, 247, 288) However, there are important limitations within the evidence base and this study is dissimilar to previous trials as, to the author’s knowledge, it is the first trial to compare GDFT and intraoperative fluid restriction.(312) Moreover, it is one of the few trials to be conducted in an otherwise optimised perioperative environment. It is notable that the most recent trials exploring GDFT within an ERAS protocol have shown either equivalent or inferior outcomes for patients randomised to the treatment arm and as such, the results of this trial can be considered congruent with recent evidence.(289, 290) The results of this study suggest that the previously
demonstrated benefits of GDFT may be offset by the other advancements in perioperative care or that whilst GDFT may be superior to liberal fluid therapy, fluid restriction may be an equally valid intraoperative fluid administration strategy. Whether GDFT will provide clinically significant benefits in an individual setting is most likely dependent on the perioperative care environment and the prevalent fluid administration regimen.

Fixed volume regimens such as fluid restriction have previously been heterogeneously defined and applied and as such, some studies have shown inferior outcomes for patients randomised to fluid restriction.\(^{(221, 223, 319)}\) It is important to appreciate that fluid restriction is essentially an avoidance of the historic practice of fluid overload.\(^{(192, 354)}\) Regardless of the terminology used, the aim of perioperative fluid administration is to maintain normovolaemia and adequate tissue perfusion. In this trial, there were no significant differences in perioperative weight gain amongst patients in both groups. Moreover, the absolute weight gain was minimal and hence unlikely to be clinically significant and causative of adverse outcomes.\(^{(224)}\) Whilst patients in the GDFT arm received slightly more colloid in the intraoperative period, it is likely that patients were able to compensate for these differences.

A potential criticism of this study is that the control group were assigned to 2L of fluid rather than a weight-based regimen. However, it is important to note that this study recommended a maximum of 2L of fluid intraoperatively and some patients received considerably less than this. This volume of fluid was the standard practice within the institution and was retained to allow comparative studies. The volumes themselves are consistent with patients receiving restrictive fluid management in other studies.\(^{(43)}\) Philosophically, the study was also about having a ‘restrictive’ but
uniform fluid regimen for all ('one small size fits all') and comparing this to targeted fluid administration so no attempt was made to individualise the restriction arm in any way. If a weight based regimen was used, it may have accentuated the differences in intraoperative fluid amount between the two groups but we would speculate that it would have lead to more protocol violations and greater amounts of fluid postoperatively by clinicians deeming it as necessary compensatory amounts.

In this study, patients randomised to GDFT had superior corrected aortic flow time without any differences in cardiac index between the groups. It is therefore possible that although flow velocity targets can be pursued, internal physiological compensation assisted by the use of vasopressors limits how much cardiac index can be optimised. This finding has not been seen in previous trials and warrants further investigation. It is possible that higher values of cardiac indices are a measure of physiological reserve rather than therapeutic targets as observed by Shoemaker and colleagues when studying supranormal targets for fluid therapy a decade ago.\textsuperscript{(228, 231)} It is also important to note that in this trial, the patients randomised to fluid restriction showed acceptable intraoperative cardiac indices. This may be a result of some of the elements of optimised perioperative care where the avoidance of oral bowel preparation and preoperative carbohydrate loading prevents dehydration and avoids resultant decreases in circulating volume. It is possible that the observed cardiac indices in both groups were adequate with further optimisation not translating into clinically significant benefits.

This study was powered for an index of surgical recovery as compared to previous trials which have been powered for hospital length of stay. Whilst this may be thought of as a limitation, it has been previously recognised that a singular intervention is unlikely to reduce hospital length of stay in an otherwise optimised
As such, a sensitive measure such as the SRS—which also correlates with physiological measures of recovery—is ideal to detect any clinically meaningful benefits obtained from interventions even if they do not result in decreased hospital length of stay. Previous use of recovery measures such as the SRS in this capacity has illustrated clinically significant benefits in the absence of decreased length of stay. An absolute difference of 20 points was selected as it was considered to be clinically significant on the basis of previous studies in our institution. Since previous studies in other settings had shown decreased morbidity and hospital length of stay from the use of the ODM, a difference of this magnitude was felt to be a reasonable expectation especially as the technology was to be potentially used in our institution following the results of this trial with the additional costs requiring justification in terms of clinically significant improvement in patient outcomes.

The primary endpoint itself was designated as the day seven SRS as it was felt that any differences in recovery trajectory should manifest by this stage and not be influenced by the other aspects of perioperative care such as epidural analgesia. It was also felt that for any improvement (or otherwise) to be considered clinically significant would require changes to manifest outside the immediate postoperative period. Previous intraoperative interventions in our setting have also shown improvements in recovery beyond the immediate postoperative period. Lastly, it should also be noted that the SRS was measured on postoperative day one and three alongside other endpoints with no changes or trends seen between any of these.

The majority of patients in this study also received epidural analgesia. Whilst epidural analgesia is considered as an important component of optimised
perioperative care, it is known to cause vascular redistribution and can influence the absolute values obtained by the ODM.(333) Nonetheless, the ODM is already used in clinical practice alongside epidurals and previous trials have also used epidural analgesia when investigating GDFT.(247, 290) Most patients in this study also received vasopressors, which would counteract vascular redistribution.

Whilst GDFT allows individualised titration of intraoperative intravenous fluids, it is possible that the simple avoidance of fluid overload in the perioperative setting is adequate for patients with physiological reserve. The results of this study are generalisable to patients undergoing colonic resection within modern perioperative care settings but this does not preclude the investigation of GDFT in other settings, where it may have a role in the care of patients who are more physiologically compromised. However, in a recent trial, patients with greater comorbidities undergoing colorectal surgery experienced adverse outcomes following GDFT.(290) It is also possible that any benefits gained from careful titration of fluids in the intraoperative setting are offset by postoperative fluid administration, which is usually conducted without the assistance of invasive monitoring. Any differences in intravenous fluid administration are also further confounded by early oral intake of fluids and solids.

This randomised trial has shown that GDFT and intraoperative fluid restriction provide equivalent outcomes for patients undergoing elective colectomy within an ERAS protocol.
8. Discussion

The preceding chapters of this thesis have discussed each experiment individually. However, a unified discussion of the findings is warranted to further delineate the findings, comment on the limitations and identify the scientific and immediate clinical implications of this work.

8.1 Overview of results

Chapter one introduced the topic of fluid administration and demonstrated its central role in perioperative care. Chapter two demonstrated the variation in perioperative care and discussed its influence on fluid administration. Chapter three evaluated fluid administration within an otherwise standardised and optimised environment. It showed that intraoperative fluid restriction was feasible in patients undergoing elective colectomy within an ERAS protocol and demonstrated that greater fluid volumes were associated with adverse clinical outcomes. This study also established that the clinical practice within the institution of study was intraoperative fluid restriction- one model of current best-practice- and could thus form a baseline against which other fluid regimens could be trialled. Chapter four began to explore the competing fluid regimen of GDFT, which has also been recommended for clinical use. It established that there was clinical interest and academic equipoise towards GDFT and the ODM and that the AUS/NZ region may provide a suitable environment for conducting further studies. Chapter five critically appraised the existing evidence pertaining to ODM-guided fluid therapy in colorectal surgery to assist in the design of future studies. It demonstrated the limitations of published trials including no direct comparison between GDFT and intraoperative fluid restriction and studies conducted within settings of heterogeneous, out-dated
perioperative care. Chapter six showed that within an environment of contemporary perioperative care, GDFT did not provide clinical benefits in major elective rectal surgery. Chapter seven showed that GDFT and intraoperative fluid restriction provided equivalent outcomes in colonic resection within an otherwise optimised perioperative care protocol.

8.2 Appraisal of findings

Perioperative fluid therapy has been subject to numerous paradigm shifts over history and recent trends within optimised perioperative care may be looked upon similarly in future years. Nonetheless, given the ubiquitous use of intravenous fluids across all surgical and medical care and the room for improvement that clearly persists, efforts in this field are worth pursuing.

The two surveys in this thesis both outlined the inherent heterogeneity in clinical attitudes and practice as it pertains to perioperative care and fluid therapy specifically. This demonstrates the difficulties in generalising the results of one setting to another. This thesis has aimed to show that fluid administration does not exist in a perioperative vacuum but is a singular intervention amongst many, all of which influence each other and the end surgical outcome. As outlined in chapter seven, a change in practice in fluid therapy will provide clinical benefits depending on the adequacy of the status quo and the other elements of perioperative care as they are implemented.

In chapter three, the important link between intraoperative and postoperative fluid therapy was demonstrated. Studies involving fluid therapy must attempt to control fluid administration outside the phase of the intervention and this study was necessary to evaluate prevalent practice in this regard. However, the majority of
studies in this field suffer from the limitation of not accounting for oral intake in the postoperative period, which affects fluid balance. The clinical implication of this is that regular weights represent the most practical method of determining fluid balance. It is notable that postoperative weights were not different between the two groups of patients in chapter seven, which may explain the lack of difference in outcomes.

Chapter five identified many methodological aspects of the published trials, which assisted in the design of the subsequent prospective studies described in this thesis. However, it is necessary to state that the prospective studies were not able to account for all of the perceived shortcomings of the previously published trials. The important progress that has been made with these studies may allow future studies to further advance our understanding of this subject. Accordingly, the work from this thesis has raised important questions with scientific and clinical implications.

8.3 Implications for future research

The surveys in chapters two and four were limited by their response rate and thus whether the results represent the opinion of the majority is unknown. Future surveys should aim for a greater response rate to increase the validity of these findings. Moreover, repeated surveys of the same population could be of some utility to outline changes in practice in response to new evidence and further explore the ‘knowing-doing’ gap.

A key area of confusion in the area of fixed volume regimens is heterogeneity in definitions with no agreement on what constitutes liberal, restrictive, traditional, judicious fluid management etc. Previous authors have proposed their own definitions and absolute values may differ between surgical settings and the
perioperative care context. (72, 192) Some consensus should be reached with regards to this matter so that future studies can clearly state their position with respect to an established standard. This will also improve the validity of cumulative meta-analysis.

Individualised fluid therapy has been driven by the goal of optimising global haemodynamics and cardiac contractility. There are several important questions that remain unanswered in this area. Whilst the prescribed goals in cardiac indices seem achievable, it is unknown whether the achievement of these goals represents therapeutic progress or a measure of physiological reserve. If the latter is true, then intraoperative cardiac indices may have value as a prognostic index. Moreover, global haemodynamic optimisation is assumed to improve the splanchnic microcirculation and this has been previously demonstrated. (200) However, whether these assumptions hold true in the context of vasopressor use and regional anaesthesia deserves investigation.

Intraoperative colloid administration with the aim of improving cardiac function is a clinical application of the Starling curve as mentioned in the introduction. This strategy aims to encourage patients to function at the very peak of the Starling curve. However, a fundamental physiological question is whether this is wise practice as it potentially exhausts any residual capacity to compensate for other stressors. The optimal point may in fact be along the midpoint of the Starling curve to prevent myocardial muscle fibres from extending to a length beyond their optimal range of contraction. This is especially important when instruments such as the ODM are used as in this instance, the final bolus is revealed as being unnecessary since the practice is terminated when stroke volume does not exceed more than ten percent, indicating the plateau of the Starling curve is reached. Thus it could be
argued that every patient who undergoes GDFT using the ODM reaches the plateau phase of the Starling curve, which could be detrimental. Other instruments which rely on stroke volume variation are not subject to this limitation as they indicate whether the recipient is fluid responsive prior to the bolus being administered.

It is also important to differentiate between the theory of GDFT and the ODM instrument. Whilst the latter is most widely used currently to conduct GDFT, there are other options available as mentioned in the introduction. This is relevant as the ODM is not completely non-invasive and is subject to a learning curve.(327) In the trial described in chapter seven, measurements were not able to be recorded for one patient and the instrument is also subject to interference from electrosurgical devices. Future developments in this field may allow for other more reliable technology to emerge. Moreover, non-invasive measures of fluid responsiveness are also required for the postoperative phase where a significant amount of intravenous fluid is administered on clinical assessment alone.

There remains the possibility that GDFT provides some unmeasured benefit when compared to fluid restriction for patients undergoing elective colorectal surgery within an optimised perioperative care setting. However, any benefit is unlikely to be clinically significant based on these and other more recent studies.(289, 290) The other possibility which warrants equally urgent investigation is the potential for harm from this intervention. This is important due to the physiological rationale outlined above and the results of more recently published trials.(289, 290) An updated meta-analysis of ODM-guided fluid therapy and GDFT in the setting of colorectal surgery is thus warranted with ideally a multi-centred trial conducted to conclusively address this hypothesis.
8.4 Implications for clinical practice

The results of this thesis do not justify a change in practice from fluid restriction to GDFT within the immediate clinical setting. Other institutions should similarly evaluate their clinical practice to determine if any changes are necessary.

The postoperative period should be continued as an area of focus as significant quantities of intravenous fluid are administered on clinical assessment alone. During the course of the clinical studies outlined in the thesis, fluid administration was more tightly regulated with simple steps such as not allowing the prescription of intravenous fluids over the phone. This practice should be continued to encourage rational clinical decision-making and emphasise the place of intravenous fluids as a medication which can cause harm when administered inappropriately.

8.5 Implications for health policy

At the risk of redundancy with the contents of chapter one, it is necessary to review the historic context of policy decisions pertaining to GDFT and ODM-guided fluid therapy in particular and evaluate how they are influenced by these studies.

Previous trials and meta-analyses formed the evidence base from which guidelines were derived which recommended the mandatory use of ODM-guided fluid therapy in all patients undergoing major abdominal surgery.(303) This resulted in the Health Technology Assessment Committee recommending the use of the ODM and the Center for Evidence Based Purchasing funding the ODM within the UK.(298, 299) In the USA, the Centers for Medicare and Medicaid similarly deemed that the use of the ODM is both “reasonable” and “necessary” for all patients undergoing major abdominal surgery and funded it.(301, 302) As ERAS protocols
are implemented across the UK, ODM-guided fluid therapy is being similarly recommended and instituted as part of the ERAS protocol.(300)

However, the studies from this thesis and others investigating ODM-guided fluid therapy within established ERAS protocols have shown either equivalent or inferior outcomes in patients randomised to ODM-guided fluid therapy.(289, 290) A potential lack of benefit is further compounded by the additional, not insignificant cost of this technology and the investments in human capital required for proper implementation.(300) Since this trial and others conducted in otherwise optimised environments have not demonstrated any benefits, with previous trials suggesting potentially harmful effects(289, 290), the widespread implementation of ODM-guided fluid therapy for major abdominal surgery should be reconsidered.
9. Conclusion

This thesis has explored the ideal fluid administration regimen in colorectal surgery within optimised perioperative care settings. It has demonstrated that fluid administration is influenced by the other aspects of perioperative care and that results from non-optimised settings may not be applicable for patients managed within an ERAS environment.

In optimised care settings, intraoperative fluid restriction and GDFT using the ODM are both thought of as optimal. There is clinical interest in both regimens and academic equipoise is split between the two. Fluid restriction has been shown to be clinically feasible within an ERAS protocol.

Prospective studies showed that both fluid restriction and GDFT provide equivalent outcomes for patients undergoing major colorectal surgery within an environment of contemporary perioperative care.

This has important clinical and health policy implications and this work has also outlined other areas of scientific importance which warrant investigation.

*The subject of water and electrolyte balance has been obscured by a long series of efforts to establish short cuts. It is not a simple subject but rather one that requires careful study and thought*

**Jonathan E. Rhoads** (1907–2002) Professor of Surgery, University of Pennsylvania, USA
Appendix 1: Patient Booklet
Oesophageal Doppler in Colon Surgery

Patient booklet

Please ask patient to fill out as below:

- Before the operation ....................... Page 4 – 7
- Day 1 in the morning ....................... Page 10 – 13
- Day 2 in the morning ....................... Page 15 – 16
- Day 3 in the morning ....................... Page 20 – 23
Before the operation
Investigating feelings of tiredness

Some things to be aware of while you complete this questionnaire:

- There are no right or wrong answers to the questions.

- It is best not to spend long thinking about any one answer; normally the first response is best.

- Some questions may seem very similar, but for measurement purposes it is often important to ask a question in slightly different ways. We would appreciate your patience and willingness to answer all of the questions.

- Please remember your answers to this questionnaire are completely confidential.

Thank you for taking the time to fill out this questionnaire
Part 1
Please think about the last two days and tick the box that best describes how you have been feeling.

### During the last two days ...

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>Almost Never</th>
<th>Some of the time</th>
<th>Fairly Often</th>
<th>Very Often</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have been feeling drained</td>
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<tr>
<td>2. I start things without difficulty then get tired</td>
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<td>3. I have been feeling energetic</td>
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<td>4. I have had trouble paying attention</td>
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<td>5. I have been feeling worn out</td>
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<tr>
<td>6. I have been feeling refreshed</td>
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<td>7. My body has been feeling heavy all over</td>
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<td>8. I have been feeling vigorous</td>
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<td>9. I have been forgetful</td>
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<td>10. It has been hard for me to get motivated to do my regular activities</td>
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### During the last two days ...

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>Almost Never</th>
<th>Some of the time</th>
<th>Fairly Often</th>
<th>Very Often</th>
<th>All of the time</th>
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</thead>
<tbody>
<tr>
<td>11. I do very little in a day</td>
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<td>12. I have been able to concentrate on things</td>
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<td>13. My thoughts have wandered easily</td>
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<td>14. I lack the energy to do things I normally do</td>
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<td>15. I have been feeling fatigued</td>
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<td>16. I have had the energy to do lots of things</td>
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<td>17. Physically, I have felt tired</td>
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<td>18. I have made more mistakes than usual</td>
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<td>19. I have had to restrict how much I try and do in a day</td>
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<td>20. I have been feeling lively</td>
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</table>
Part 2

The following questions ask how much fatigue interferes with the things you can do.

For activities you are not doing, for reasons other than fatigue, tick the box labelled "N/A" (not applicable).

Examples of why you might tick the "N/A" box include:
- You are still in hospital and are not required to do things like run errands.
- You are not the person who usually cooks in your household.
- Or, you have a wound that is vacuum-sealed and you are not able to do household chores because of this.

### During the last two days, I have had enough energy to...

<table>
<thead>
<tr>
<th>Activity</th>
<th>Not at all</th>
<th>Only occasionally</th>
<th>Sometimes, but less than usual</th>
<th>Nearly as often as usual</th>
<th>As often as usual</th>
<th>N/A</th>
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</thead>
<tbody>
<tr>
<td>21. Read a newspaper/book or watch TV</td>
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<td>22. Bath/wash</td>
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<td>23. Dress</td>
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<td>24. Do household chores</td>
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<td>25. Cook</td>
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<tr>
<td>26. Work</td>
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<td>27. Visit or socialize with family and friends</td>
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<tr>
<td>28. Engage in leisure or recreational activities</td>
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<tr>
<td>29. Shop or do errands</td>
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<td>30. Walk</td>
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<td>31. Exercise other than walk</td>
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</tbody>
</table>
Preop: Please fill this out before your operation
Circle the appropriate answer or write in the space provided.

1. How would you describe your pain level at the present time, \textit{while in bed}?  
\begin{tabular}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline
No & Moderate & Severe \\
Pain & Pain & Pain \\
\end{tabular}

2. How would you describe your pain level at the present time, \textit{when you move}?  
\begin{tabular}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline
No & Moderate & Severe \\
Pain & Pain & Pain \\
\end{tabular}

3. How would you describe your pain level at the present time, \textit{when you cough}?  
\begin{tabular}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline
No & Moderate & Severe \\
Pain & Pain & Pain \\
\end{tabular}

4. How would you describe your energy levels at the present time?  
\begin{tabular}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline
Fit & Slightly & Tired & Fatigued \\
Tired & Tired & Tired \\
\end{tabular}

5. How would you describe your level of \textit{nausea} at present time?  
0. No nausea at all  
1. Mild, tolerable nausea  
2. Moderate nausea, requiring medication  
3. Severe nausea  
\begin{tabular}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline
Nil & Mild & Moderate & Severe \\
\end{tabular}

6. Have you vomited in the past 6 hrs?  
0. No  
1. Yes, only once  
2. Yes 2-3 times  
3. Yes more than 3 times

Doppler Patient Booklet v 1 / Feb 08
7. At the present time, do you feel...

Hungry?

1  2  3  4  5  6  7  8  9  10
Not Hungry
At all  Moderately Hungry  Very Hungry

Thirsty?

1  2  3  4  5  6  7  8  9  10
Not Thirsty
At All  Moderately Thirsty  Very Thirsty

8. How would you describe your anxiety level at present time?

1  2  3  4  5  6  7  8  9  10
Very Relaxed  Moderately Anxious  Very Anxious

9. How would you rate your Sleep quality over the past 24 Hrs?

1  2  3  4  5  6  7  8  9  10
No Sleep  Moderate Sleep  Excellent Sleep

10. How would you rate the quality of the care you have received thus far?

1  2  3  4  5  6  7  8  9  10
Poor  Moderate  Excellent

11. Did you pass flatus today?  _____  Did you last pass flatus yesterday?  _____

12. Did you pass a bowel motion today?  _____  Did you pass a bowel motion yesterday?  _____

13. Did you have a full solid meal today?  _____  Did you have a full solid meal yesterday?  _____

Deppler Patient Booklet v 1 / Feb 08
After the operation
On the morning of:
Day 1
Part 1
Please think about the last two days and tick the box that best describes how you have been feeling.

### During the last two days ...

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</tbody>
</table>

### During the last two days ...

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>Almost</th>
<th>Some of the time</th>
<th>Fairly</th>
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<td>19. I have had to restrict how much I try and do in a day</td>
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20. I have been feeling lively

Part 2

The following questions ask how much fatigue interferes with the things you can do.

For activities you aren’t doing, for reasons other than fatigue, tick the box labelled “N/A” (not applicable).

Examples of why you might tick the “N/A” box include:
- You are still in hospital and are not required to do things like run errands.
- You are not the person who usually cooks in your household.
- Or, you have a wound that is vacuum-sealed and you are not able to do household chores because of this.

During the last two days, I have had enough energy to...

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How would you describe your overall energy levels at the present time on a scale from 1 to 10?

1  2  3  4  5  6  7  8  9  10

Fit  Slightly Tired  Tired  Fatigued
Day 1: Please fill this out on the morning after the day of the operation
Circle the appropriate answer or write in the space provided.

1. How would you describe your pain level at the present time, while in bed?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
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<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pain</td>
<td>Moderate Pain</td>
<td>Severe Pain</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

2. How would you describe your pain level at the present time, when you move?

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<th>3</th>
<th>4</th>
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</tr>
</tbody>
</table>

3. How would you describe your pain level at the present time, when you cough?

<table>
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<tr>
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<th>3</th>
<th>4</th>
<th>5</th>
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<td></td>
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</table>

4. How would you describe your energy levels at the present time?

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<thead>
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<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fr</td>
<td>Slighty Tired</td>
<td>Tired</td>
<td>Fatigued</td>
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</tbody>
</table>

5. How would you describe your level of nausea at present time?

0. No nausea at all
1. Mild, tolerable nausea
2. Moderate nausea, requiring medication
3. Severe nausea

<table>
<thead>
<tr>
<th></th>
<th>1</th>
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<th>3</th>
<th>4</th>
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<th>10</th>
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</thead>
<tbody>
<tr>
<td>NI</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
<td></td>
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</table>

6. Have you vomited in the past 6 hrs?

0. No
1. Yes, only once
2. Yes 2-3 times
3. Yes more than 3 times
7. At the present time, do you feel...

Hungry?

1 2 3 4 5 6 7 8 9 10
Not Hungry At all Moderately Hungry Very Hungry

Thirsty?

1 2 3 4 5 6 7 8 9 10
Not Thirsty At All Moderately Thirsty Very Thirsty

8. How would you describe your anxiety level at present time?

1 2 3 4 5 6 7 8 9 10
Very Relaxed Moderately Anxious Very Anxious

9. How would you rate your Sleep quality over the past 24 Hrs?

1 2 3 4 5 6 7 8 9 10
No Sleep Moderate Excellent Sleep

10. How would you rate the quality of the care you have received thus far?

1 2 3 4 5 6 7 8 9 10
Poor Moderate Excellent

11. Did you pass flatus today? _____ Did you pass flatus after your op yesterday? _____

12. Did you pass a bowel motion today? _____ Did you pass one after your op yesterday? _____

13. Did you have a full solid meal today? _____ Did you have one after your op yesterday? _____

14. Did you walk independently today? _____ Did you walk independently after your op yesterday? _____
On the morning of: Day 2
Day 2: Please fill this out on the morning of day 2 after the operation
Circle the appropriate answer or write in the space provided.

1. How would you describe your pain level at the present time, while in bed?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
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<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Moderate</td>
<td>Severe</td>
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2. How would you describe your pain level at the present time, when you move?

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3. How would you describe your pain level at the present time, when you cough?

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<tr>
<td>Full</td>
<td>Slightly Tired</td>
<td>Tired</td>
<td>Fatigued</td>
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Doppler Patient Booklet V 1 / Feb 08

15
7. At the present time, do you feel...

Hungry?

1  2  3  4  5  6  7  8  9  10
Not Hungry
At all
Moderately
Hungry
Very
Hungry

Thirsty?

1  2  3  4  5  6  7  8  9  10
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Relaxed
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1  2  3  4  5  6  7  8  9  10
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14. Did you walk independently today? ______ Did you walk independently yesterday? ______
On the morning of:
Day 3
Part 1
Please think about the last two days and tick the box that best describes how you have been feeling.

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<th></th>
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<tr>
<td>1. I have been feeling drained</td>
<td></td>
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<tr>
<td>2. I start things without difficulty then get tired</td>
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<td>3. I have been feeling energetic</td>
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<td>4. I have had trouble paying attention</td>
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<td>5. I have been feeling worn out</td>
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<tr>
<td>6. I have been feeling refreshed</td>
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<tr>
<td>7. My body has been feeling heavy all over</td>
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<td>8. I have been feeling vigorous</td>
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<td>9. I have been forgetful</td>
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<td>10. It has been hard for me to get motivated to do my regular activities</td>
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Examples of why you might tick the “N/A” box include:
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- Or, you have a wound that is vacuum-sealed and you are not able to do household chores because of this.

During the last two days, I have had enough energy to...  

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How would you describe your overall energy levels at the present time on a scale from 1 to 10?

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<th>1</th>
<th>2</th>
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<tr>
<td>Fit</td>
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<td>Slightly Tired</td>
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<td>Tired</td>
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<td>Fatigued</td>
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</table>

Dopple Patient Booklet v 1 / Feb 08
Day 3: Please fill this out on the morning of day 3 after the operation
Circle the appropriate answer or write in the space provided.

1. How would you describe your pain level at the present time, *while in bed*?
   
   ![Pain level scale](1-10)

   No  Moderate  Severe
   Pain  Pain  Pain

2. How would you describe your pain level at the present time, *when you move*?
   
   ![Pain level scale](1-10)

   No  Moderate  Severe
   Pain  Pain  Pain

3. How would you describe your pain level at the present time, *when you cough*?
   
   ![Pain level scale](1-10)

   No  Moderate  Severe
   Pain  Pain  Pain

4. How would you describe your energy levels at the present time?
   
   ![Energy level scale](Fit - Fatigued)

   Fit  Slightly Tired  Fatigued

5. How would you describe your level of nausea at present time?
   
   0. No nausea at all
   1. Mild, tolerable nausea
   2. Moderate nausea, requiring medication
   3. Severe nausea

   ![Nausea level scale](1-10)

   Nil  Mild  Moderate  Severe

6. Have you vomited in the past 6 hrs?
   
   0. No
   1. Yes, only once
   2. Yes 2-3 times
   3. Yes more than 3 times
7. At the present time, do you feel...

Hungry?

1 2 3 4 5 6 7 8 9 10

Not Hungry At all Moderately Hungry Very Hungry

Thirsty?

1 2 3 4 5 6 7 8 9 10

Not Thirsty At All Moderately Thirsty Very Thirsty

8. How would you describe your anxiety level at present time?

1 2 3 4 5 6 7 8 9 10

Very Relaxed Moderately Anxious Very Anxious

9. How would you rate your sleep quality over the past 24 hrs?

1 2 3 4 5 6 7 8 9 10

No Sleep Moderately Excellent Sleep

10. How would you rate the quality of the care you have received thus far?

1 2 3 4 5 6 7 8 9 10

Poor Moderate Excellent

11. Did you pass flatus today? _____ Did you last pass flatus yesterday? _____

12. Did you pass a bowel motion today? _____ Did you pass a bowel motion yesterday? _____

13. Did you have a full solid meal today? _____ Did you have a full solid meal yesterday? _____

14. Did you walk independently today? _____ Did you walk independently yesterday? _____
## Oesophageal Doppler Study - Consent Form

<table>
<thead>
<tr>
<th>English</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maori</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cook Iwi</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fijian</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ni-Vanuatu</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Samoan</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tokelauan</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tongan</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
| Other languages to be added following consultation with nearest relative/relative.

3.1 I have read and I understand the information sheet dated _______ for volunteers taking part in the study designed to assess whether Oesophageal Doppler monitoring improves outcomes following colon surgery. I have had the opportunity to discuss this study with the answers I have been given.

3.2 I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.

3.3 I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care or continuing health care.

3.4 I have had this project explained to me by ____________.

3.5 I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.

3.6 I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.

3.7 I understand the compensation provisions for this study.

3.8 I have had time to consider whether to take part.

3.9 I know who to contact if I have any side effects to the study.

3.10 I know who to contact if I have any questions about the study.

Doppler Patient Booklet v 1 / Feb 08
4.1 I agree to an approved auditor appointed by either the ethics committee, or the regulatory authority or their approved representative, and approved by the Northern Y Ethics committee reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.

4.2 I consent to the researchers storing a specimen of my blood (or other tissue) for its later use as a part of this study YES/NO

4.3 I consent to blood samples being destroyed at the end of the study. YES/NO

4.4 I consent to blood samples being sent to Middlemore Hospital Laboratory YES/NO

4.10 I wish to receive a copy of the results YES/NO

Alternatively “I would like the researcher to discuss the outcomes of the study with me”. YES/NO

4.11 I agree to my GP or other current provider being informed of my participation in this study/the results of my participation in this study YES/NO

5. I __________________(full name) hereby consent to take part in this study.

Date
Signature

Full names of Researchers:
Associate Professor Andrew C. Hill
Dr Sanjaya Sunavasa

Contact Phone Number for researchers:
AF Hill- 09 2760444 ext 8424
Dr Sunavasa 021 774647

Project explained by
Project role
Signature
Date
Oesophageal Doppler Study
Participant Information

Associate Professor Andrew Hill, Department of Surgery, Middlemore Hospital - Phone 09-776 6044 ext 4424

Introduction
You are invited to take part in a clinical research study. Your participation is entirely voluntary (your choice). You do not have to take part in this study and if you choose not to take part this will not affect any future care or treatment.

About the study
A successful outcome from surgery is dependent on many factors. Most doctors agree that successful surgery is a combination of excellent care before, during and after surgery. As knowledge about the human body increases, we have developed many strategies to enhance a patient's recovery.

People undergoing surgery are normally starved. To prevent dehydration and compensate for blood loss during surgery, they are given intravenous (via the vein) fluids. Traditionally, doctors estimate the amount of fluids and on some occasions patients receive too much or too little fluid. Too much or too little fluid can make the heart pump less strongly. An Oesophageal (Foodpipe) Doppler probe is a soft instrument which is placed in the mouth during surgery (after the patient is asleep) to directly measure heart function. This allows doctors to give fluid more accurately.

We are inviting you to participate in our new study. We wish to investigate whether giving fluids more accurately using an Oesophageal Doppler probe during surgery decreases complications, increases energy levels after surgery and increases the speed of recovery.

We are planning to invite 80 patients who are going to have colon operations to take part in this study. If you agree to participate, you will be randomly (by chance) assigned to receive fluids during surgery either according to Oesophageal Doppler measurements or according to existing practices (as described above). The probe will be placed regardless of which group you are assigned to. Before and after surgery, you will have the same routine, standardised care plan as all the other patients and your participation in this trial will not affect the standard of care in any way. Participation in this study will not prevent you from having Oesophageal Doppler Monitoring in the future. It will not prevent you from having any other healthcare in the future.

The anaesthetist looking after you during surgery will place the probe into your mouth after you are asleep and will take it out before you wake up. The probe will only be used during surgery. It will be connected to a computer monitor that will display readings of heart function. Anaesthetists will give fluid based on these readings.

After surgery, we will ask you to complete a set of questionnaires with the assistance of researchers. These will ask you about pain and energy levels. We will also test your hand grip strength and your breathing. None of these tests are painful.

Patients undergoing surgery routinely have blood tests before and after surgery for monitoring purposes. If you agree, we wish to collect about 4ml extra blood each time (Total of 3 times = approximately 12ml blood total). We will collect this blood at the same time as your routine blood tests and hence you will not have extra blood tests.

Participants must note some feel May disagree with the teaching of the head associated with probe placement as it is considered uncomfortable for research purposes and may wish to seek advice before consenting. However, it is acknowledged that individuals have the right to choose to participate.
About Oesophageal Doppler

The Oesophageal Doppler is a device that provides minute-to-minute information on heart function using ultrasound technology. Ultrasound technology is very safe as it uses sound waves and is used in pregnant ladies. The probe is soft and thus unlikely to cause physical damage to teeth, gums or the floor of the mouth. It has already been used in over 500,000 patients to administer fluid. The probe used is disposable and new ones will be used for each patient.

Risks

The probe could cause damage to teeth, gums, mouth or throat. You may not get the exact amount of fluid even with the help of the Oesophageal Doppler recordings. A new, sterile probe will be used for each patient but there is still a small chance of infection. There will be no costs or payments to you in order to participate in this study.

Participation

Your participation is entirely voluntary (your choice). You do not have to take part in this study. This will not affect your treatment in any way. If you do agree to take part you are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your continuing health care.

General

Further information can be obtained from Dr Sanjai Srivastava, Department of Surgery (Tel 276 0044 ext 2100 or 021 774647)

An interpreter will be provided if you would like one. You may have a friend, family, or whanau support to help you understand the risks and benefits of this study and any other explanation you may require.

Advocacy

If you have any queries or concerns regarding your rights as a participant in this research study, you can contact an independent Health and Disability Advocate. This is a free service provided under the Health & Disability Commissioner Act.

Telephone (NZ wide): 0800 555 050
Free Fax (NZ wide): 0800 2787 7878 (0800 2 SUPPORT)
Email: advocacy@adc.org.nz

Confidentiality

No material which could personally identify you will be used in any reports on this study. Your hospital records are confidential. Your name or any other personally identifying information will not be used in reports or publications resulting from this study. The information about your medical history and medications required to interpret the research results will be identified using a code to ensure your confidentiality.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is automatic and your case will be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you will not get any compensation. This depends on a number of factors such as whether you are an energy or non-energy ACC claimant. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

Results

Doppler Patient Booklet v 1 / Feb 08
The final results of the research will not be known until December 2010. At the conclusion of the study, results will be made available by mail to those who have requested this on the consent form. However, if you are not sure about whether you have requested the study results, you can contact Dr. Srinivasan, Research Fellow, Middlemore Hospital (ph. 09 2760644 ext 2100).

Statement of Ethical Approval: This study has received ethical approval from the Northern Y Regional Ethics Committee.
Appendix 2: Postoperative Follow-up Form

Please fill this form out on __________________________

Thank you very much for all your help with this, and I wish you all the best.

Investigating tiredness

Some things to be aware of while you complete this questionnaire:

- There are no right or wrong answers to the questions.

- It is best not to spend long thinking about any one answer, normally the first response is best.

- Some questions may seem very similar, but for measurement purposes it is often important to ask a question in slightly different ways. We would appreciate your patience and willingness to answer all of the questions.

- Please remember your answers to this questionnaire are completely confidential.

Thank you for taking the time to fill out this questionnaire
### Part 1
Please think about the last two days and tick the box that best describes how you have been feeling.

#### During the last two days …

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Almost Never</th>
<th>Some of the time</th>
<th>Fairly Often</th>
<th>Very Often</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have been feeling drained</td>
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<td>2. I start things without difficulty then get tired</td>
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<td>3. I have been feeling energetic</td>
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<td>4. I have had trouble paying attention</td>
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<td>5. I have been feeling worn out</td>
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<td>6. I have been feeling refreshed</td>
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<td>7. My body has been feeling heavy all over</td>
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<td>8. I have been feeling vigorous</td>
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<td>9. I have been forgetful</td>
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<td>10. It has been hard for me to get motivated to do my regular activities</td>
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</table>

#### During the last two days …

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Almost Never</th>
<th>Some of the time</th>
<th>Fairly Often</th>
<th>Very Often</th>
<th>All of the time</th>
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</thead>
<tbody>
<tr>
<td>11. I do very little in a day</td>
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<td>12. I have been able to concentrate on things</td>
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<tr>
<td>13. My thoughts have wandered easily</td>
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<td>14. I lack the energy to do things I normally do</td>
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<tr>
<td>15. I have been feeling fatigued</td>
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<td>16. I have had the energy to do lots of things</td>
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<td>17. Physically, I have felt tired</td>
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<td>18. I have made more mistakes than usual</td>
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<td>19. I have had to restrict how much I try and do in a day</td>
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<td>20. I have been feeling lively</td>
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</table>
**Part 2**

The following questions ask how much fatigue interferes with the things you can do.

For activities you aren’t doing, for reasons other than fatigue, tick the box labelled “N/A” (not applicable).

Examples of why you might tick the “N/A” box include:
- You are still in hospital and are not required to do things like run errands.
- You are not the person who usually cooks in your household.
- Or, you have a wound that is vacuum-sealed and you are not able to do household chores because of this.

### During the last two days, I have had enough energy to...

<table>
<thead>
<tr>
<th>Activity</th>
<th>Not at all ▼</th>
<th>Only occasionally ▼</th>
<th>Sometimes but less than usual ▼</th>
<th>Nearly as often as usual ▼</th>
<th>As often as usual ▼</th>
<th>N/A ▼</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. Read a newspaper/book or watch TV</td>
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<td>22. Bath/wash</td>
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<tr>
<td>23. Dress</td>
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<tr>
<td>24. Do household chores</td>
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<tr>
<td>25. Cook</td>
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<tr>
<td>26. Work</td>
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<td>27. Visit or socialize with family and friends</td>
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<tr>
<td>28. Engage in leisure or recreational activities</td>
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<tr>
<td>29. Shop or do errands</td>
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<tr>
<td>30. Walk</td>
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<tr>
<td>31. Exercise other than walk</td>
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</table>

How would you describe your overall energy levels at the present time on a scale from 1 to 10?

![Energy Level Scale](image)

D7 questionnaire Sentar v.1 10/03/2009

3
Circle the appropriate answer or write in the space provided.

1. How would you describe your pain level at the present time, \textit{while in bed}?

\begin{center}
\begin{tabular}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
No & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline \\
Pain & Moderate & Severe \\
\end{tabular}
\end{center}

2. How would you describe your pain level at the present time, \textit{when you move}?

\begin{center}
\begin{tabular}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
No & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline \\
Pain & Moderate & Severe \\
\end{tabular}
\end{center}

3. How would you describe your pain level at the present time, \textit{when you cough}?

\begin{center}
\begin{tabular}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
No & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline \\
Pain & Moderate & Severe \\
\end{tabular}
\end{center}

4. How would you describe your energy levels at the present time?

\begin{center}
\begin{tabular}{cccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \\
Fit & Slightly & Tired & Fatigued \\
\hline \\
\end{tabular}
\end{center}

5. How would you describe your level of nausea at present time?

0. No nausea at all \\
1. Mild, tolerable nausea \\
2. Moderate nausea, requiring medication \\
3. Severe nausea

\begin{center}
\begin{tabular}{cccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \\
Nil & Mild & Moderate & Severe \\
\hline \\
\end{tabular}
\end{center}

6. Have you vomited in the past 6 hrs?

0. No \\
1. Yes, only once \\
2. Yes 2-3 times \\
3. Yes more than 3 times
7. At the present time, do you feel…

Hungry?

1  2  3  4  5  6  7  8  9  10
Not Hungry At all Moderately Hungry Very Hungry

Thirsty?

1  2  3  4  5  6  7  8  9  10
Not Thirsty At all Moderately Thirsty Very Thirsty

8. How would you describe your anxiety level at present time?

1  2  3  4  5  6  7  8  9  10
Very Relaxed Moderately Anxious Very Anxious

9. How would you rate your Sleep quality over the past 24 Hrs?

1  2  3  4  5  6  7  8  9  10
No Sleep Moderate Excellent Sleep

10. How would you rate the quality of the care you have received thus far?

1  2  3  4  5  6  7  8  9  10
Poor Moderate Excellent

11. How many days after your operation did you return to work / normal activity?

__________
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