UNIVERSITY OF SOUTHERN QUEENSLAND

EARLY VERSUS TRADITIONAL POSTOPERATIVE NUTRITIONAL PROVISION IN GASTROINTESTINAL RESECTIONAL SURGERY PATIENTS: A META-ANALYSIS

A Dissertation submitted by

Emma Jane Osland, BHSc (Nutr & Diet) (Hons)

For the award of

Master of Philosophy

October 2009

Abstract

The purpose of the current work was to conduct a meta-analysis of randomized controlled trials evaluating the effect on surgical outcomes of providing nutrition within 24-hours following gastrointestinal or abdominal surgery compared with traditional postoperative management. A search of all available electronic databases was conducted to identify randomized controlled trials published comparing the outcomes of early and traditional postoperative feeding. Trials involving resection of portions of the gastrointestinal tract followed by patients receiving nutritionally significant oral or enteral intake within 24-hours after surgery were included for analysis. Random effects meta-analyses were performed. Outcome variables analysed were mortality, total complications, anastomotic dehiscence, length of stay, nausea and vomiting, nasogastric tube reinsertion, days to passing flatus, and days to first bowel motion. Fifteen studies involving a total of 1240 patients were analysed. A significant reduction in relative odds of developing post operative complications was seen in patients receiving early postoperative feeding (Odds Ratio (OR) 0.55; 95% Confidence Interval (CI) 0.35, 0.87; p=0.01). Trends favouring early feeding were seen with relation to reduction in mortality (OR 0.71; CI 0.32, 1.56; p= 0.39), anastomotic dehiscence (OR 0.75; CI 0.39, 1.4; p=0.39), length of stay (Weighted Mean Difference (WMD) -1.28; CI -2.94, 0.38; p=0.13), development of nausea and vomiting (OR0.93, CI 0.53, 1.65), resumption of bowel function as evidenced by days to passage of flatus (WMD -0.42; CI -1.12, 0.28; p=0.23) and first bowel motion (WMD -0.28; CI -1.20, 0.64; p=0.55) however these were not statistically significant. A forty-eight percent relative increase in nasogastric tube reinsertion was seen with early feeding practices (OR 1.48; CI 0.93, 2.35; p=0.10). Early provision of nutritionally significant oral or enteral intake appears to be associated with a significant reduction in reported complications when compared with traditional postoperative feeding practices and might confer reductions in mortality, anastomotic dehiscence, and resumption of gastrointestinal function as evidenced by passage of flatus. Based on the current evidence, surgeons can be reassured regarding the safety of early postoperative feeding. The widespread adoption of this evidence-based practice would be anticipated to translate to better perioperative outcomes for patients undergoing elective surgical procedures and more cost-effective management strategies for the institutions providing surgical care.

CERTIFICATION OF DISSERTATION

I certify that the ideas, investigations, results, analyses, and conclusions reported in this dissertation are entirely my own work except for where acknowledged otherwise. I also certify that the work is original and has not been previously submitted for any other award.

____________________________ __________________

Signature of Candidate Date

ENDORSEMENT

____________________________ __________________

Signature of Supervisor Date

____________________________ __________________

Signature of Supervisor Date

Acknowledgements

I wish to acknowledge the following people for their contributions to the current work and preparation of the dissertation.

Associate Professor Shahjahan Khan for his guidance with the statistics underpinning this research including direction provided throughout the coursework undertaken (STA2300-Data Analysis); making himself available for regular meetings and consultation throughout my studies; provision of assistance and feedback on this dissertation, seminar presentation and manuscript prepared based on this research; assistance with the submission of this dissertation; and assistance in organising my commencement at USQ .

Professor Muhummed Ashraf Memon for his encouragement to convert a workplace project into formalised study and award; assistance with understanding the surgical and statistical concepts involved in this work; comments and feedback on drafts of the dissertation, seminar presentation and manuscript prepared based on this research; making himself available for meetings and consultation throughout my studies.

Ms Rossita Muhummed Yunus for performing the statistical tests and generating the forest and funnel plots presented.

Dr Kim Vidhani (Consultant Anaesthetist, Princess Alexandra Hospital) for reviewing sections 2.6.3.2 Anaesthetic Practice and 2.6.3.4 Postoperative Analgesia for accuracy.

Ms Louise Mitchell (Senior Physiotherapist, Ipswich Hospital) for reviewing section 2.6.3.5 Early Mobilisation for accuracy.

Dr Shelley Wilkinson (Conjoint Senior Research Dietitian/Nutritionist, Mater Mothers' Hospital & Griffith University School of Public Health) for proofreading the final draft of the dissertation.

Ms Marion Hogg for making it possible to have time off work when required for study purposes.

The staff of the Faculty of Sciences, specifically the Department of Mathematics and Computing, at USQ for their support of this research.

The University of Southern Queensland for allocating me a place in the Research Training Scheme.

Table of Contents

List of Figures

List of Tables

Chapter 1 Introduction

Nutrition is an important aspect of perioperative care for patients undergoing surgery (Sobotka *et al*., 2004). Preoperative nutritional status, such as significant weight loss or pre-existing malnutrition, has been recognised for over 70 years for its association with adverse postoperative outcomes (Studley, 1936). Patients undergoing gastrointestinal surgery frequently present with malnutrition due to the presence of symptoms such as loss of appetite, early satiety, nausea, vomiting and diarrhoea associated with the condition indicating surgical intervention (Hall, 2006; McCullum and Polisena, 1999; Ward, 2003). Furthermore, the physiological stress induced by surgery creates a hypermetabolic response which results in protein catabolism and the redistribution of adipose tissue and muscle from body stores for use by more metabolically active tissues such as the liver, bone and visceral organs (Brunicardi, 2005; Champe and Harvey, 1994; Grimble, 2008). This process may lead to or exacerbate weight loss and underlying nutritional deficits in patients (Holte and Kehlet, 2002). In cases of severe malnutrition, delaying the required surgery may be indicated until a period of pre-operative nutritional support has been undertaken to minimise the operative risks (Torosian, 1999).

Traditional perioperative care for many surgeries, including the resection of parts of the gastrointestinal tract, involves preoperative fasting from midnight or early morning of the day of surgery, gastric decompression via a nasogastric tube and withholding nutritional provision postoperatively until resumption of bowel function. Bowel function is considered to have returned once flatus or the first postoperative bowel motion has been passed, however this may not occur for close to a week after surgery in many cases (Correia and da Silva, 2004; Nygren *et al*., 2003; Way, 1988). Reasons purported for traditional practice include reducing the risk of postoperative abdominal distension (Nelson *et al*., 2007), nausea and vomiting (Casto *et al*., 2000; Nelson *et al*., 2007; Nygren *et al*., 2003) and subsequent concerns regarding anastomotic dehiscence, wound dehiscence and pulmonary aspiration (Casto *et al*., 2000; Nelson *et al*., 2007). Moreover, when dietary intervention is recommenced, fluids of limited nutritional value such as water, tea, lemonade, consommé soups and jelly are traditionally provided for the first several days until tolerance is thought to be established (Hancock *et al*., 2002). This may result in a patient receiving little or no nutrition within the first week following surgery, further contributing to the caloric deficit incurred during the perioperative period, exacerbating the catabolism and malnutrition experienced by this already nutritionally vulnerable patient group (Hancock *et al*., 2002).

For these reasons perioperative nutritional management has been hypothesized to play a vital role in optimising the recovery of and outcomes experienced by patients undergoing elective gastrointestinal surgery (Nygren *et al*., 1998; Sobotka *et al*., 2004; Soop, 2003). There are also secondary financial implications for the institutions in which the surgery is being performed as cost savings are associated with reduced complications and duration of hospital stay, both of which may be facilitated by the adoption of these perioperative feeding practices (Ljungqvist *et al*., 1998; Sagar *et al*., 1979; Tsunoda *et al*., 2005; Zhou *et al*., 2006).

In light of this, the concept of early postoperative enteral feeding (defined as feeding commenced within 24-hours following surgery or on the first postoperative day) was introduced into the surgical literature around 30 years ago (Sagar *et al*., 1979). This represents a paradigm shift in thinking, allowing enteral or oral intake before bowel function has returned, and often in the absence of a nasogastric tube for gastric decompression traditionally used routinely to avoid nausea and vomiting (Nelson *et al*., 2007). In the 30 years since the first randomised controlled trial (RCT) investigating the risks and benefits of early postoperative feeding in gastrointestinal surgery patients (Sagar *et al*., 1979), there have been no less than 30 RCTs investigating this topic (Aiko *et al*., 2001; Beier-Holgersen and Boesby, 1996, 1998; Bickel, Shtamler and Mizrahi, 1992; Binderow *et al*., 1994; Carr *et al*., 1996; de Aguilar-Nascimento and Goelzer, 2002; Delaney *et al*., 2003; Feo *et al*., 2004; Gabor *et al*., 2005; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Henriksen *et al*., 2002a; Henriksen *et al*., 1998; Henriksen *et al*., 2002b; Heslin *et al*., 1997; Hiratsuka *et al*., 2003; Hochwald *et al*., 1997; Lassen *et al*., 2008; Lucha *et al*., 2005; Malhotra *et al*., 2004; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Reissman *et al*., 1995; Ryan *et al*., 1981; Schroeder *et al*., 1991; Singh *et al*., 1998; Smedley *et al*., 2004; Stewart *et al*., 1998; Tsunoda *et al*., 2005; Watters *et al*., 1997; Zhou *et al*., 2006). Results of these studies have collectively failed to support the traditional postoperative management principles, and many demonstrate clear benefits associated with early feeding in terms of nutritional (Beier-Holgersen and Boesby, 1998; Carr *et al*., 1996; Henriksen *et al*., 2002a; Henriksen *et al*., 2002b; Hochwald *et al*., 1997; Malhotra *et al*., 2004; Ryan *et al*., 1981; Sagar *et al*., 1979; Singh *et al*., 1998), biochemical (Aiko *et al*., 2001; Beier-Holgersen and Boesby, 1996; Hochwald *et al*., 1997), anthropometric (Beier-Holgersen and Boesby, 1996; Henriksen *et al*., 2002b; Malhotra *et al*., 2004; Sagar *et al*., 1979; Schroeder *et al*., 1991), financial (Nessim *et al*., 1999) and clinical outcomes (Beier-Holgersen and Boesby, 1996; Binderow *et al*., 1994; Carr *et al*., 1996; de Aguilar-Nascimento and Goelzer, 2002; Delaney *et al*., 2003; Feo *et al*., 2004; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Henriksen *et al*., 2002b; Heslin *et al*., 1997; Lassen *et al*., 2008; Lucha *et al*., 2005; Malhotra *et al*., 2004; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Reissman *et al*., 1995; Ryan *et al*., 1981; Sagar *et al*., 1979; Schroeder *et al*., 1991; Singh *et al*., 1998; Smedley *et al*., 2004; Stewart *et al*., 1998; Tsunoda *et al*., 2005; Zhou *et al*., 2006).

In addition to early postoperative feeding, the concept of allowing oral consumption of carbohydrate rich fluids up to two hours prior to induction of anaesthesia has also been proposed as an additional strategy to improve nutritional outcomes (Noblett *et al*., 2006; Nygren *et al*., 1998; Soop *et al*., 2001; Yuill *et al*., 2005).

Meta-analysis is a statistical method increasingly reported in the medical literature to establish with statistical confidence the risks and benefits of a particular treatment or intervention (Davey Smith *et al*., 1997; Egger and Smith, 1997; Egger *et al*., 1997a). It offers the advantage of integrating the results of independent clinical trials investigating comparable interventions by determining an average effect size for the combined data. This allows data from small studies, that alone offer limited guidance to clinical practice, to be incorporated into evidence-based recommendations (Davey Smith *et al*., 1997; Egger and Smith, 1997; Egger *et al*., 1997a). To date, three meta-analyses have been undertaken in an attempt to strengthen the claims in support of early feeding (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). While the results of these fail to demonstrate benefit of traditional practice or a foundation for fears of adverse clinical outcomes conventionally attributed to early feeding, there are a number of limitations with these analyses that may limit the validity of the outcomes and conclusions reported. Firstly, studies that include immune-enhancing enteral feed products (Impact® [Nestle Nutrition, Minneapolis, USA]) were not excluded from their analysis (Heslin *et al*., 1997). These products are fortified with arginine, glutamine, nucleic acids, antioxidants and/or omega-3 fatty acids and have been independently associated with a reduced risk of postoperative complications, wound infections and hospital length of stay (LOS) in elective surgical oncology patients (Braga *et al*., 2002; Braga *et al*., 1999; Zheng *et al*., 2007). Therefore failure to exclude studies using immune-enhancing products as their early feeding intervention may confound the study results and limit the conclusions that can be made about early feeding's effect on postoperative infections and LOS. It should be noted, however, that recent clinical studies investigating such products have not consistently supported the conclusions of these earlier studies with regards to these clinical benefits (Klek *et al*., 2008; Lobo *et al*., 2006).

Secondly, up to 10% of the patients in these meta-analyses received nutrition distal to the anastomosis (Beier-Holgersen and Boesby, 1996; Heslin *et al*., 1997; Sagar *et al*., 1979; Watters *et al*., 1997). Given that fear of anastomotic dehiscence has been cited as a primary reason for avoidance of early feeding, failure to exclude studies in which feeding occurs distal to the anastomosis undermines the ability to comment on the benefit or harm posed by early feeding with regard to anastomotic dehiscence and may confound results obtained.

Thirdly, one study included in these meta-analyses permitted clear fluid diets as their early feeding intervention (Reissman *et al*., 1995). As clear fluid diets are nutritionally inadequate, it is impossible to meet nutritional requirements irrespective of the quantity of diet consumed, due to the absence or grossly inadequate provision of protein, lipids and many micronutrients (Hancock *et al*., 2002). As one of the objectives of early feeding is to provide postoperative nutrition to allow healing and recovery, it is of vital importance that a balanced, nutritionally complete intake be provided within the early feeding period, and the absence of this in some of the included studies weakens the analyses as a whole.

Fourthly, the literature review undertaken for these meta-analyses appear to have been inadequate as a number of studies that meet their documented inclusion criteria have been omitted from these analyses. The study by Feo *et al* (Feo *et al*., 2004) was excluded in all three meta-analyses (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001) as *"both treatment groups were allowed liquid diet, therefore [there was] no control group to early feeding"* (Andersen *et al*., 2006, p.12). The cited paper, however, clearly states liquid diet in the nil-by-mouth group was only provided after passage of flatus (Feo *et al*., 2004), thereby meeting the stated inclusion criteria of each analysis. Furthermore, at least five eligible studies readily locatable via Pubmed and Embase database searches do not appear to have been identified in their searches (Han-Geurts *et al*., 2001, 2007; Lucha *et al*., 2005; Nessim *et al*., 1999; Zhou *et al*., 2006).

Fifthly, while both fixed and random effects models are reported in the most recent meta-analysis (Lewis *et al*., 2008), only the former is reported in the earlier publications (Andersen *et al*., 2006; Lewis *et al*., 2001). The fixed effect model of meta-analysis assumes a shared common effect size while a random effects model allows for a distribution of true effect size (Borenstein *et al*., 2007). Thus random effects models are more appropriately applied to meta-analyses in clinical fields where it is improbable all studies will have identical true effect sizes due to unavoidable diversity in clinician practices and patient demographics (Borenstein *et al*., 2007). Given some of the fundamental differences among the interventions in the included studies and the potential impact these may have on treatment effects, a random effects model is a more suited model for use with the studies included in these meta-analyses (Egger *et al*., 1997a).

In view of the limitations of the currently available meta-analyses on this topic, the primary objectives of the current work are to produce a meta-analysis that:

- Includes studies where diets of comparable nutritional composition were provided in the early stages post surgery, and that the location of provision was proximal to the surgical anastomosis;
- Utilises thorough literature review techniques to exhaust all applicable databases ensuring all eligible studies are included; and
- Applies a random effects model of meta-analysis to better reflect the nature of the interventions being pooled and assessed.

Point estimates for binary and continuous outcomes will be summarised using odds ratios and weighted mean differences respectively. Confidence intervals will be calculated for the mean effects and the statistical significance of results will be assessed using *P*-values at a significance level of 0.05. Forest plots will be constructed to present the point estimates: continuous variables will be presented in their natural scale while binary variables will be presented in logarithmic scales so as to facilitate visual interpretation. Heterogeneity will be assessed using the Q statistic and I^2 index, and funnel plots will be constructed to assess the presence of any publication bias.

It is hypothesised that a meta-analysis that places a stronger emphasis on the nutritional and statistical considerations affecting the outcomes associated with postoperative feeding practices will provide more methodologically robust evidence to support or refute the safety and benefits attributed to early postoperative feeding when compared with traditional postoperative nutritional care. This is an important contribution to evidence-based practice in medicine, and as such, informs best-practice within surgical care. It also serves to provide reassurance for surgeons regarding the safety of early feeding and thus to facilitate changes to current practices that are strongly steeped in medical tradition. Ultimately, it is hoped that the results will guide changes to practice that will translate into better perioperative outcomes for patients undergoing elective surgical procedures, and more cost-effective management strategies for the institutions providing surgical care.

Chapter 2 Literature review

2.1 History of Nutritional Recommendations in Surgery

From the early stages of modern surgical history, pre- and postoperative nutritional care has been recognised as having an important impact on patient outcomes. Dietary recommendations dating back to 1761 demonstrate the use of dietary preparation for one to two weeks preoperatively for management of conditions such as gallstones (Guys Hospital, 1761).

2.1.1 Postoperative Nil-By-Mouth and Delayed Postoperative Feeding

Withholding nutrition from patients until the resolution of the transient postoperative ileus has been employed as the standard postoperative nutritional management for well over 100 years (Casto *et al*., 2000). This practice is thought to have developed in response to the high rates of postoperative emesis experienced by patients anaesthetised with traditional agents such as ether and chloroform (Bufo *et al*., 1994). From this origin, a cautious reintroduction of diet following operative procedures has been adopted, irrespective of the site of surgery, and particularly so if it has involved the gastrointestinal tract (Bufo *et al*., 1994). A 1915 surgical after-treatment textbook recommends *"feed[ing] the patient as soon as possible, but at the same time to avoid distension"* for patients undergoing abdominal surgery (Todd, 1915, p.35). A clear fluid diet (consisting of water, tea and sparkling wine) was promoted in the first few days post surgery followed by boiled fish or eggs after *"a day or two"* (Todd, 1915, p.37). The addition of other elements such as dairy and 'farinaceous' [starchy] foods are recommended to be *"cautiously added"* after a few days on a light protein di*et al*lowing the *"gradual return made to a full mixed diet"* (Todd, 1915, p. 38). Similar concepts were promoted into the 1930s with dietary intake being limited to milk diluted with limewater allowed from the third or fourth postoperative day, once flatus had been passed (Bufo *et al*., 1994).

By the 1940s a more rapid progression through the dietary stages appeared in surgical texts, however little in terms of dietary composition or reasoning behind the provision of this had changed. A textbook from 1940 advises to avoid oral nutrition within the first 24-hours post surgery so as not to 'interfere with' the anticipated paralytic ileus resulting from physical manipulation of the bowel, and to commence milk and water orally after one day, then solids 48-hours thereafter (Wakely and Hunter, 1940). Another source recommends of *"giving water in the first twelve hours, then liquids for the next twenty-four hours, and thereafter a light diet until the bowels have moved"* following abdominal and thoracic surgery (Mullally, 1947, p.134). Even within the last 20 years these recommendations have been largely adhered to and promoted (Way, 1988).

2.1.2 Development of the Concept of Early Postoperative Feeding in Elective Surgery

The recognition of a high prevalence of nutritional deficits and malnutrition occurring in patients requiring elective surgical management (Howard and Ashley, 2003; Torosian, 1999), along with the subsequent improvements in these conditions following nutritional support (Sobotka *et al*., 2004; Torosian, 1999), led to the beginning of a change in practice to perioperative nutritional management in the 1970s. Delaney *et al* (1977) published an uncontrolled trial in which a high protein elemental nutritional product was provided via jejunostomy to 19 patients who had undergone major upper gastrointestinal surgery (oesophageal, gastric or pancreatic resections) within in five to six days of surgery: favourable outcomes were associated with this practice although these were not quantified in the published paper. Further to this report Sagar *et al* (1979) undertook the first randomised controlled trial (RCT) investigating the clinical outcomes of early postoperative feeding in 1978, utilising a diluted elemental feed product provided on the first postoperative day through a nasojejunal tube to thirty patients receiving a variety of gastrointestinal surgeries, including oesophagogastrectomies, colectomies and abdominoperitneal resections. In a feeding regimen that provided the intervention group with up to 1000kcal per day by the second postoperative day and up to 1600kcal per day by the second half of the first postoperative week (compared with <500kcal per day in the control group), it was demonstrated that early postoperative feeding significantly reduced weight loss and hospital length of stay (LOS) (Sagar *et al*., 1979). Although both groups showed considerable nitrogen losses postoperatively, the patients receiving jejunal feeding demonstrated a less negative nitrogen balance than those in the control group (Sagar *et al*., 1979).

Following the success of these interventions, the literature shows a steady development in the concept of early postoperative feeding that demonstrates a progression from providing diluted elemental feed products (Ryan *et al*., 1981; Sagar *et al*., 1979) to allowing whole protein formulas into the jejunum (Beier-Holgersen and Boesby, 1996; Carr *et al*., 1996; Schroeder *et al*., 1991), to oral liquids (Hartsell *et al*., 1997; Zhou *et al*., 2006), to full diet from the day of surgery (Binderow *et al*., 1994; Delaney *et al*., 2003; Han-Geurts *et al*., 2001, 2007; Lucha *et al*., 2005; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Stewart *et al*., 1998).

2.2 Beneficial Outcomes Associated With Early Feeding in Elective Gastrointestinal Surgery

Beneficial outcomes have been associated with early postoperative feeding. These are outlined below in terms of outcome variables. The characteristics of the studies suggesting these benefits are summarised in Table 2.1.

2.2.1 Mortality

Early feeding, irrespective of form [tube feeding (Beier-Holgersen and Boesby, 1996), fluids (Hartsell *et al*., 1997) or solid food (Han-Geurts *et al*., 2007; King *et al*., 2006; Stewart *et al*., 1998)] does not appear to be associated with increased postoperative mortality in studies where this is reported. While perioperative deaths are often observed, differences in mortality between intervention groups do not reach statistical significance (Beier-Holgersen and Boesby, 1996; Han-Geurts *et al*., 2007; Hartsell *et al*., 1997; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Reissman *et al*., 1995; Sagar *et al*., 1979; Stewart *et al*., 1998). Only one study reports a statistically significant increase in mortality in patients receiving early feeding, however death in all cases were reported to have occurred *before* the commencement of early oral intake (Han-Geurts *et al*., 2001).

Table 2.1 – Studies Reporting Benefit Associated with Early Feeding

Author	Study Methodology	Patient population	n (cont/int)	Primary postoperative intervention	Outcome attributed to early feeding reaching statistical significance
Basse *et al* (2002)	Prospective Controlled Trial	Elective right hemicolectomy or sigmoid colon resection	14/14	Fast-track vs traditional approach	• Earlier resumption of bowel function • Reduced LOS
Beier-Holgersen *et al* (1996)	RCT	Gastrointestinal disease treated with bowel resection with anastomosis, enterostomy, gastric (*n*=5) or oesophageal resection (*n*=3)	30/30	Early feeding vs NBM	• Earlier flatus • Reduced LOS • Reduced complications • Reduced infective complications
Carr *et al* (1996)	RCT	Unspecified intestinal surgery	14/14	Early feeding vs NBM	• Increased caloric intake • Reduced nitrogen losses
Delaney *et al* (2003)	RCT	Segmental intestinal or rectal resection by laparotomy, including reoperation or pelvic surgery and those with comorbidities	33/31	Early feeding and early mobilisation vs NBM	• Reduced LOS
Di Fronzo *et al* (2003)	Observational study	Elective open colorectal surgery	-/87	Early feeding vs NBM	• Short LOS
Han-Geurts *et al* (2001)	Multi-centred RCT	Abdominal surgery (vascular + colonic)	49/56	Early feeding at will vs NBM	• Earlier resumption of normal diet
Han-Geurts *et al* (2007)	Multi-centred RCT	Open colorectal surgery	50/46	Early feeding at will vs NBM	• Earlier tolerance of oral diet
Henriksen *et al* (2002b)	RCT	Elective colorectal surgery	20/20	Fast-track vs traditional approach	• Increased caloric intake • Increased nitrogen intake • Improved muscle function

Hur *et al* (2009)	Prospective Controlled Trial	Gastrectomy for malignancy	31/35	Early feeding (day 3 post op) vs NBM	• Earlier flatus • Reduced LOS
King *et al* (2006)	Prospective trial with historical control	Laparoscopic or open colorectal resections	86/60	Fast-track vs traditional approach	• Reduced LOS
Lassen *et al* (2008)*	Multi-centred RCT	Hepatic, pancreatic, oesophageal, gastric resections; bilioenteric and gastroenteric bypass procedures that would be traditionally indicated for NBM postoperative management	227/220 (enteral feeding/ food at will)	Early jejunal feeding vs early oral feeding at will *No NBM control group	• Less overall complications with early oral diet; earlier passage of flatus with early oral diet; • Reduced LOS with early oral diet
Nessim *et al* (1999)	RCT	Anorectal reconstructive surgery	27/27	Early feeding vs NBM + loperamide	• Earlier first bowel motion
Raue *et al* (2004)	Prospective Controlled Trial	Laparoscopic sigmoidectomy	29/23	Fast-track vs traditional approach	• Earlier oral intake • Reduced time to first bowel motion • Reduced LOS
Reissman *et al* (1995)	RCT	Open colorectal surgery	81/80	Early feeding vs NBM	• Earlier tolerance of oral diet
Ryan *et al* (1981)	RCT	Partial colectomy	7/7	Early feeding vs NBM	• Reduced duration of IV fluid provision • Reduced weight loss at 2 and 4 weeks postop • Increased caloric intake • Increased nitrogen intake
Sagar *et al* (1979)	RCT	Major intestinal surgery – oesophagogastrectomy (*n*=2), gastrectomy (*n*=6), colectomy, anterior resection, abdominoperineal resection	15/15	Early feeding vs NBM	• Reduced weight loss • Reduced LOS • Increased caloric intake • Reduced nitrogen losses

Schroeder *et al* (1991)	RCT	Small or large bowel resections or reanastomosis – colonic resection, abdominoperineal resection, ileoanal J pouch, small bowel resection	16/16	Early feeding vs NBM	• Increased caloric intake • Increased nitrogen intake • Improved wound healing
Stewart *et al* (1998)	RCT	Colorectal resection with anastomosis and without stoma formation	40/40	Early feeding vs NBM	• Earlier commencement of solid/full diet • Earlier flatus • Earlier first bowel motion
Tsunoda *et al* (2005)	RCT	Open colorectal surgery for malignancy	13/13	Early feeding + early mobilisation vs traditional management	• Reduced time to flatus • Reduced weight loss • Reduced LOS
Zhou *et al* (2006)	RCT	Excision and anastomosis for colorectal tumour	155/161	Early feeding vs NBM	• Reduced complications • Reduced pulmonary infection • Reduced fevers • Earlier flatus • Earlier bowel motion • Reduced LOS

Con=control group; int=intervention group; RCT=Randomised Controlled Trial; NBM=Nil By Mouth; LOS=Length of (hospital) Stay; IV=intravenous; NGT=nasogastric tube

2.2.2 *Surgical Complications*

2.2.2.1 *Total and Infective Complications*

While postoperative complications are commonly reported in both traditional and early feeding groups after elective gastrointestinal surgery, most studies fail to demonstrate a statistically significant difference in the incidence of either infective or general complications between groups (Basse *et al*., 2004; Carr *et al*., 1996; Delaney *et al*., 2003; Feo *et al*., 2004; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Hur *et al*., 2009; Lassen *et al*., 2008; Lucha *et al*., 2005; Ortiz *et al*., 1996b; Reissman *et al*., 1995; Sagar *et al*., 1979; Stewart *et al*., 1998; Tsunoda *et al*., 2005). Two studies that reported significant differences describe increased complications in the traditional management groups thereby suggesting better outcomes are achieved with early feeding. Beier-Holgersen *et al* (1996) reported increased rates of total and infectious complications in their control group compared with early feeding (p=0.0089 and p=0.009 respectively), while Zhou *et al* (2006) reported increased pulmonary infections (p=0.034), febrile illness (p=0.042) and pharyngolaryngitis (p<0.001) in their delayed feeding group who retained their nasogastric tubes until resumption of bowel function was demonstrated.

2.2.2.2 *Anastomotic Dehiscence*

Anastomotic dehiscence is a major complication following gastrointestinal surgery resulting in adverse outcomes such as increased morbidity, mortality, LOS, cost, and in the case of surgery for malignant disease, increased rate of cancer recurrence (Kingham and Pachter, 2009). The incidence of anastomotic dehiscence in the literature ranges from 1% to 30%, with rates of 3% to 6% considered acceptable for colorectal surgery (Kingham and Pachter, 2009). Despite long held concerns that early feeding increases the likelihood of this complication (Casto *et al*., 2000), anastomotic dehiscence was reported to not be significantly associated with the early provision of nutrition in any study that included this outcome (Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Hur *et al*., 2009; Lassen *et al*., 2008; Lucha *et al*., 2005; Reissman *et al*., 1995; Sagar *et al*., 1979; Stewart *et al*., 1998; Zhou *et al*., 2006).

2.2.3 *Length of Hospital Stay*

The effect of early feeding on the LOS in hospital is inconclusive. Some studies that investigated the effect of early feeding as their primary intervention show non-statistically significant trends toward earlier discharge (Beier-Holgersen and Boesby, 1996; Hartsell *et al*., 1997; Nessim *et al*., 1999; Stewart *et al*., 1998). Others demonstrate clinically and statistically significant reductions in LOS associated with early nutritional provision (Hur *et al*., 2009; Sagar *et al*., 1979; Tsunoda *et al*., 2005; Zhou *et al*., 2006). Still others demonstrate no difference between the early feeding and traditional groups (Binderow *et al*., 1994; Carr *et al*., 1996; Feo *et al*., 2004; Han-Geurts *et al*., 2007; Lucha *et al*., 2005; Reissman *et al*., 1995). More consistent decreases in LOS are observed in studies that investigate early feeding in association with other interventions in a multimodal approach to postoperative care suggesting a greater effect on this outcome when multiple strategies are employed (Basse *et al*., 2004; Delaney *et al*., 2003; King *et al*., 2006; Raue *et al*., 2004).

Furthermore, a recent RCT comparing the effect of early oral versus early jejunal feeding suggests that the route of nutritional provision may be as important as timing on LOS outcomes (Lassen *et al*., 2008). Statistically significant earlier hospital discharge was found to be associated with commencement of full diet on the first postoperative day when compared with jejunal feeding in patients receiving major upper gastrointestinal surgery (Lassen *et al*., 2008).

2.2.4 Cost Savings

It stands to reason that there should be cost-benefit advantages to providing nutrition early in the postoperative period if this results in reduced complications and shorter LOS. However of the studies that investigated the economic impact of early feeding, none demonstrate statistically significant differences in hospital costs associated with early feeding interventions (Beier-Holgersen and Boesby, 1996; Feo *et al*., 2004; Hur *et al*., 2009; King *et al*., 2006; Lucha *et al*., 2005; Nessim *et al*., 1999). A trend toward a modest reduction in the cost of hospital admission was reported in some studies (King *et al*., 2006; Nessim *et al*., 1999).

2.2.5 Earlier Resumption of Bowel Function

Early nutritional provision has been frequently associated with earlier resumption of bowel function, as evidenced by passage of flatus (Beier-Holgersen and Boesby, 1996; Binderow *et al*., 1994; Henriksen *et al*., 2002b; Hur *et al*., 2009; Reissman *et al*., 1995; Schroeder *et al*., 1991; Stewart *et al*., 1998; Zhou *et al*., 2006) and/or time to first bowel motion (Basse *et al*., 2004; Beier-Holgersen and Boesby, 1996; Carr *et al*., 1996; Henriksen *et al*., 2002b; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Ryan *et al*., 1981; Schroeder *et al*., 1991; Stewart *et al*., 1998; Tsunoda *et al*., 2005; Zhou *et al*., 2006). However this only reached statistically significance in five studies (Beier-Holgersen and Boesby, 1996; Hur *et al*., 2009; Nessim *et al*., 1999; Stewart *et al*., 1998; Tsunoda *et al*., 2005; Zhou *et al*., 2006). Other studies showed comparable outcomes between early and traditional feeding groups with relation to time to return of bowel function (Feo *et al*., 2004; Han-Geurts *et al*., 2007).

2.2.6 Tolerance of Early Feeding

Traditionally, early reintroduction of nutrition following surgery has been avoided in the belief that a postoperative ileus resulting from physical manipulation of the bowel and operative stress would result in intolerance of oral diet (Casto *et al*., 2000). However studies utilising early oral feeding have reported tolerance with rates of 80% to 90% from the first or second postoperative day (Di Fronzo *et al*., 1999; Hartsell *et al*., 1997; Ortiz *et al*., 1996b; Reissman *et al*., 1995; Stewart *et al*., 1998) and 100% of patients tolerating diet in one study (Tsunoda *et al*., 2005). Consequently, all studies that reported this outcome describe solid food being consumed and tolerated significantly earlier than in traditional feeding groups (Han-Geurts *et al*., 2001, 2007; Raue *et al*., 2004; Reissman *et al*., 1995; Stewart *et al*., 1998). Similarly for patients who were provided early nutrition via a feeding tube, tolerance was generally high with 75% to 100% of patients experiencing no adverse gastrointestinal or tube-related events to limit nutritional provision (Beier-Holgersen and Boesby, 1996; Carr *et al*., 1996; Schroeder *et al*., 1991).

2.2.7 *Nutritional Outcomes*

2.2.7.1 Caloric Intake

In all studies that investigated the nutritional intake of patients, early feeding has been associated with a significantly higher caloric intake at the end of the study period (Carr *et al*., 1996; Henriksen *et al*., 2002a; Ryan *et al*., 1981; Sagar *et al*., 1979; Schroeder *et al*., 1991). Ryan *et al* (1981) recorded nearly a 1500kcal average daily difference by the tenth postoperative day (p<0.005), while 800kcal, 1100kcal and over 600kcal daily differences between intervention groups were reported on the fourth, fifth and seventh postoperative days by Schroeder *et al* (1991), Carr *et al* (1996) and Sagar *et al* (1979) respectively. Henriksen *et al* (2002b) reported an average difference of 21kJ/kg in intake by the fifth postoperative day between intervention groups. It is more common for studies providing tube feeding as the nutritional intervention to report caloric intake (Carr *et al*., 1996; Ryan *et al*., 1981; Sagar *et al*., 1979; Schroeder *et al*., 1991): only one study providing early oral nutrition reported this data (Henriksen *et al*., 2002a).

2.2.7.2 Nitrogen and Protein Intake

Similarly, higher nitrogen intake (Carr *et al*., 1996; Henriksen *et al*., 2002b; Ryan *et al*., 1981; Sagar *et al*., 1979; Schroeder *et al*., 1991) and more positive nitrogen balances have been observed in the early feeding intervention groups of studies that reported this outcome (Carr *et al*., 1996; Sagar *et al*., 1979). Average nitrogen intake was significantly higher (14.1±2.73g vs 3.4±1.44g, p<0.005) at the tenth postoperative day in the early fed patients in the Ryan *et al* (1981) study when compared with patients receiving traditionally management. Similar results were demonstrated by Carr *et al* (1996), in which the protein provision of 60.6±14.4g in patients receiving early feeding compared with 0.8±0.2g in those with conventional care translated to significant differences in nitrogen balance on the first postoperative day (5.3±2.7g vs -13.2±11.6g, p<0.005), although these differences had resolved by the fifth postoperative day (1.2±1.2g vs 1.0±0.8g, NS). Sagar *et al* (1979) demonstrated that only patients treated with early feeding had achieved a positive nitrogen balance by the seventh postoperative day.

2.2.7.3 Postoperative Weight Loss

The nutritional intake in patients receiving early postoperative feeding has been shown to translate into improved weight outcomes. Ryan *et al* (1981) demonstrated significantly less weight loss in the patients receiving early feeding. By the fourth postoperative week patients receiving early feeding had lost 2.8±1.16% of their preoperative body weight while those being managed in the traditional manner lost 6.1±1.35% (p<0.005) of their initial body weight (Ryan *et al*., 1981). Similarly, at one week post surgery Sagar *et al* (1979) reported a median weight loss of 0kg (1kg lost to 5.3kg gained) compared with 1.85kg (5.8kg lost to 0.5kg gained) (p<0.01). Trends in reduced weight loss that did not reach statistical significance were also reported by Schroeder *et al* (1991) and Tsunodo *et al* (2005).

2.2.7.4 Body Composition

Several authors have also investigated the effect of postoperative weight loss on body composition and found no significant differences in protein, fat or water losses at one or two weeks (Henriksen *et al*., 2002a; Schroeder *et al*., 1991), or up to two months postoperatively (Henriksen *et al*., 2002a). No differences have been observed between interventions with regard to skin-fold thickness or mid-arm muscle area at five days following surgery (Schroeder *et al*., 1991). In the context of a multimodal program, Basse *et al* (2002) demonstrated reductions in femur lean body mass and fat mass in the early feeding group compared with a conventional treatment group. No differences were seen in peripheral muscle strength as evidenced by grip strength (Carr *et al*., 1996; Henriksen *et al*., 2002b; Schroeder *et al*., 1991). Henrikson *et al* (2002b) report reduced loss of muscular strength in their colorectal patients managed with an accelerated recovery program compared with traditional management as measured by voluntary knee extension which was significant at one week (p=0.04), one month (p=0.002) and two months (p=0.02) post surgery.

2.2.8 Biochemical Parameters

Serum albumin is commonly considered an indication of nutritional status, however given its role as a negative acute phase response protein it is not an accurate nutritional indicator in surgical patients (Bahn, 2006). Nevertheless Hur *et al* (2009), Carr *et al* (1996) and Ryan *et al* (1981) have reported on postoperative serum albumin levels at the first, third and fifth postoperative day, the fifth postoperative day, and second and fourth postoperative weeks respectively: no significant differences were reported between early feeding and traditional management groups. Basse *et al* (2002) found a significant decrease in albumin levels post surgery in their conventional care patients, while this was not observed in those managed within an enhanced recovery program. They also measured serum C-Reactive Protein levels as an indicator of systemic inflammation and acute phase response but found no significant differences between their intervention groups (Basse *et al*., 2002). A recent study on patients receiving gastrectomies for curative management of adenocarcinoma of the stomach also investigated the effect of early postoperative feeding on serum lymphocyte levels. However, despite trends favouring improved lymphocyte response in the early feeding group this did not reach statistical significance (Hur *et al*., 2009).

2.2.9 Quality of Life and Fatigue Levels

Three studies evaluated self-reported quality of life in patients at various time points following surgery to determine if early feeding altered patient perception of the postoperative experience, however no differences have been reported between traditional and early feeding groups at any time point (Delaney *et al*., 2003; Feo *et al*., 2004; Han-Geurts *et al*., 2007). A further three studies evaluated postoperative fatigue levels from seven days to three months postoperatively and similarly found no difference between intervention groups (Henriksen *et al*., 2002b; Raue *et al*., 2004; Schroeder *et al*., 1991).

2.2.10 Wound Healing

One study investigated the effect of early postoperative feeding on wound healing as evidenced by the degree of hydroxyproline present on Gortex tubing that had been placed subcutaneously into the non-dominant upper arm during the operation (Schroeder *et al*., 1991). By the seventh postoperative day significantly higher levels of hydroxyproline were found to be present in the early feeding group when compared with those managed traditionally (p=0.02) suggesting the important role of nutrition in facilitating timely collagen deposition and thus wound healing (Schroeder *et al*., 1991).

2.3 Adverse Outcomes Associated With Early Feeding in Elective Gastrointestinal Surgery

Several adverse outcomes have been associated with early feeding, including respiratory complications, nausea and vomiting. These are outlined below.

2.3.1 Respiratory Complications

One study has suggested that significant negative outcomes are associated with early postoperative feeding. Watters *et al* (1997) conducted a RCT comparing the provision of jejunal feeds 6-hours following major elective surgery (oesophagectomy and pancreaticoduodenectomy procedures) and withholding nutritional intake until diet was recommenced on the sixth postoperative day. The primary outcome measure used was the effect of early feeding on respiratory and peripheral muscle function. Thirty-one patients (n=15 early feeding; n=16 delayed feeding) were included in the study and no differences were seen between participants at baseline (Watters *et al*., 1997). While no differences between groups were seen with regard to grip strength, maximal inspiratory pressure, LOS, postoperative complications or weight loss in the postoperative period, a 25 to 29% lower vital capacity (p<0.05) and 18 to 27% reduced forced expiratory volume (p=0.07) was noted in the early feeding group when compared with traditional management (Watters *et al*., 1997). While some measure of reduction in these respiratory parameters are expected following abdominal and thoracic operations, the differences observed in this study were unexpected and resulted in the early termination of the study due to concerns that reduced vital capacity and forced expiratory volumes may have led to the development of respiratory complications (Watters *et al*., 1997). The authors proposed abdominal distension due to early enteral feeding (experienced by 62% of patients) impaired diaphragmatic function and was a possible causative factor for their observations, and the routine practice of early feeding in this patient group was not recommended (Watters *et al*., 1997). It should be noted, however, that this study was conducted in predominantly well nourished patients with 78% of the study sample receiving an assessment of 'A-well nourished' on a preoperative Subjective Global Assessment (Watters *et al*., 1997). This is significant as early feeding is well recognised to benefit patients with pre-existing malnutrition (Sobotka *et al*., 2004; Torosian, 1999) and as such, this high proportion of well nourished patients within the sample may have resulted in the study being underpowered to demonstrate marked benefits of early postoperative nutritional. Similarly, outcomes were only measured to the sixth postoperative day (Watters *et al*., 1997) and a longer time frame may have been required to detect improvements in functional recovery following major elective surgery facilitated by early feeding, particularly given the well nourished study population.

Henrikson *et al* (2002b) and Raue *et al* (2004) also report on postoperative respiratory function in their investigations of early feeding in the context of multimodal accelerated recovery programs in colorectal surgery patients, however, neither demonstrated the detrimental outcomes describe by Watters *et al* (1997). Henrikson *et al* (2002b) conducted a RCT on 40 patients (*n*=20 traditional practice; *n*=20 multimodal program) and reported no significant differences seen in forced expiratory volume or forced vital capacity on postoperative days three or seven between groups. Similarly, no significant differences were noted between groups (*n*=29 standard care, *n*=23 multimodal approach) in the Raue *et al* (2004) controlled prospective evaluation. It should be noted, however, that these two studies utilised a multimodal accelerated recovery program in which early feeding was one of multiple interventions provided with the goal of reducing postoperative complications (Henriksen *et al*., 2002b; Raue *et al*., 2004). Furthermore, the Henriksen *et al* (2002b) and Raue *et al* (2004) studies included patients undergoing colorectal surgery utilising minimally invasive surgical techniques resulting in patients receiving surgical incisions less likely to impact negatively on respiratory function than in the Watters *et al* (1997) study. Therefore the observed effect of on respiratory function may be more related to the site of surgical incision than early feeding.

2.3.2 Nausea, Vomiting and Requirement of Nasogastric Reinsertion

Postoperative nausea (with or without vomiting) and the subsequent requirement for replacement of a nasogastric tube was the only adverse complication frequently reported in the studies investigating early feeding (Binderow *et al*., 1994; Feo *et al*., 2004; Hartsell *et al*., 1997; Nessim *et al*., 1999; Reissman *et al*., 1995). Furthermore meta-analyses on this topic have demonstrated a significantly increased relative risk ratio (RR) of postoperative vomiting with early feeding compared with traditional postoperative management (RR 1.27; 95% Confidence Interval (CI) 1.01,1.61; *p*=0.04) (Andersen *et al*., 2006; Lewis *et al*., 2001). Despite the increased nasogastric intubation and vomiting reported in the pooled results for patients being fed earlier, there has been no increase in the development of pneumonia in these patients (Andersen *et al*., 2006; Lewis *et al*., 2001). Similarly, no individual study reported increased rates of pulmonary complications associated with early feeding (Basse *et al*., 2002; Beier-Holgersen and Boesby, 1996; Binderow *et al*., 1994; Carr *et al*., 1996; Feo *et al*., 2004; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Lucha *et al*., 2005; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Raue *et al*., 2004; Reissman *et al*., 1995; Ryan *et al*., 1981; Schroeder *et al*., 1991; Stewart *et al*., 1998; Tsunoda *et al*., 2005). One study, however, reported a significantly higher rate of pulmonary infections in the traditional feeding group (Zhou *et al*., 2006).

2.4 Early Postoperative Feeding in Emergency Gastrointestinal Surgery

In recent years the concept of early postoperative feeding has also been studied in patients receiving emergency surgery for gastrointestinal perforations and consequent peritonitis (Malhotra *et al*., 2004; Singh *et al*., 1998). The aetiology of the perforations requiring emergency surgery included gastric, peptic or duodenal ulcers, typhoid fever, tuberculosis, gastric volvulus, Zollinger-Ellison syndrome, malignancy and trauma (Malhotra *et al*., 2004; Singh *et al*., 1998). In these situations, provision of nutrition within 24- to 48-hours of surgery either through a nasogastric (Malhotra *et al*., 2004) or jejunostomy (Singh *et al*., 1998) was shown to be safe and associated with reduced septic morbidity (Singh *et al*., 1998), weight loss and improved nitrogen balance (Malhotra *et al*., 2004) when compared with conventional management of withholding nutrition until evidence of resumed bowel function is seen. This suggests early feeding following emergency gastrointestinal surgery is safe and conveys similar benefits as those seen in elective gastrointestinal surgery.

2.5 Meta-analysis in Medicine

While the results of single studies, such as those discussed above, supply useful clinical information there are often limitations to the clinical guidance they can provide. Single studies may be too small and underpowered to detect small but clinically relevant treatment effects and thus may not provide reliable evidence on which to base clinical practice (Egger and Smith, 1997; Sheldon, 1999). It is expensive, time consuming and logistically difficult to undertake studies of sufficient magnitude to demonstrate with certainty small but important treatment effects (Egger and Smith, 1997). One possible solution to this clinical dilemma is the statistical method of meta-analysis which was first utilised in the evaluation of therapeutic interventions in the mid-1950s, underwent further development during the 1970s in the social sciences, and has since been employed with increasing regularity in a wide range of clinical sciences (Egger and Smith, 1997; Sutton and Higgins, 2008).

Meta-analysis has been described as "*a statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be 'combinable'*" in which the primary aim is attaining an estimate of average effect size attributable to a certain intervention presented in the same metric (Davey Smith *et al*., 1997; Egger and Smith, 1997, p.1371; Huedo-Medina *et al*., 2006). Weighting is assigned to each study using the inverse variance to adjust for study size so that information obtained from larger studies with greater precision influence the pooled results more strongly (Borenstein *et al*., 2007).

In a sense, meta-analysis is an 'observational study of the evidence' or a 'study of studies' in which the units under investigation shift from the individual to the findings of studies taken as a whole (Egger and Smith, 1997; Egger *et al*., 1997a; Greenland, 1994). Thus, it requires the same methodological rigor that is applied to other forms of research (Egger *et al*., 1997a). The methodology to produce a robust meta-analysis has been described in detail by the Cochrane Collaboration (Higgins and Green, 2006c).

While the terms 'meta-analysis' and 'systematic review' are often used interchangeably in the literature, they are not equivalent terminology (Ng *et al*., 2006). A systematic review uses the structured methodology followed to conduct a meta-analysis but lacks the statistical amalgamation of the quantitative data provided (Egger and Smith, 1997; Ng *et al*., 2006). In this sense, a meta-analysis is a further step that may be conducted as part of a systematic review if the reported data permit (Ng *et al*., 2006). Conversely, in circumstances where a meta-analysis is not possible a systematic review may *"represent the best available method to synthesise the current literature"* (Ng *et al*., 2006, p.1126). Examples of where this may be the case include the presence of significant heterogeneity or when an inadequate number of studies are located for inclusion (Ng *et al*., 2006).

Well conducted meta-analyses offer considerable benefit to the clinical sciences over narrative or systematic reviews or single studies (Davey Smith and Egger, 1998; Egger and Smith, 1997). By providing a more objective evaluation of already available data, meta-analysis may assist in understanding differences in observations between studies and clarifying resultant clinical debate (Egger and Smith, 1997; Higgins and Green, 2006a). It allows data from studies evaluating similar interventions, which on their own provide limited reliable evidence due to their small size and variability in methodological quality or outcomes, to be combined with other study results to collectively demonstrate intervention outcomes with confidence (Egger and Smith, 1997; Higgins and Green, 2006a). In this way, performing a meta-analysis may provide a greater level of precision in estimation of treatment effects than can be achieved through individual studies (Higgins and Green, 2006a). Meta-analysis also provides a more objective and reproducible approach to reporting conclusions attained from review processes (Egger and Smith, 1997). The ability to generalise study results to other populations is also a potential benefit of the meta-analysis technique (Egger and Smith, 1997). Moreover, it has the potential to stimulate research in areas where evidence is shown to be lacking while offering insight and guidance into the design and magnitude of the studies required to demonstrate treatment effects with adequate statistical power (Davey Smith and Egger, 1998; Egger and Smith, 1997; Higgins and Green, 2006a; Olkin, 1994).

However, the procedure of meta-analysis is not without its limitations. A poorly conducted meta-analysis may provide unreliable and misleading results (Egger *et al*., 1997a). The pooling of biases from multiple sources inherent in the included studies and within the processes used to conduct the meta-analysis remains a major criticism of the procedure (Ng *et al*., 2006). These issues are described in detail in sections 2.5.3 to 2.5.8.

2.5.1 Presentation of Results in a Meta-analysis

Meta-analysis results are reported numerically as summary statistics and presented graphically as forest plots. These are described below.

2.5.1.1 Summary Statistics

The type of information being reported determines the effect measures that are used to report the outcomes of the meta-analysis (Higgins and Green, 2006a). Binary outcomes such as mortality or complications may use RR, odds ratios (OR), or risk differences/absolute risk reduction to express outcomes (Higgins and Green, 2006a). The former two describe the relative effect of an intervention by comparing the risk of the investigated outcome in the intervention group with the risk of the outcome in the control group, using either risk or odds respectively (Higgins and Green, 2006a). By comparison, risk difference reports the actual difference in the risk of an event occurring between intervention and control group, allowing an estimation of the probability of the event occurring in an individual patient (Higgins and Green, 2006a).

For continuous variables, such as time or weight, weighted mean difference (WMD) or standardised mean difference (SMD) may be used to describe the average difference between interventions (Higgins and Green, 2006a). WMD is used when the scales of all studies are the same or can be converted into the same scale, such as reporting weight in pounds or kilograms (Higgins and Green, 2006a). The SMD is required when the same outcome is measured using differing scales that cannot be converted: it produces a unit-less outcome allowing all trials to be compared with each other, and is obtained by dividing the difference in mean outcome between groups by the standard deviation of the outcome among participants (Higgins and Green, 2006a).

2.5.1.2 Forest Plots

Forest plots are the standard method used to graphically present the data obtained from a meta-analysis (Higgins and Green, 2006b; Petrie and Sabin, 2000). They provide a visual summary of the effect sizes and confidence intervals of each contributing study as well as the combined effect size estimate obtained from the meta-analysis (Higgins and Green, 2006b; Petrie and Sabin, 2000).

Treatment effects are plotted on the horizontal axis, and a line vertical to the horizontal axis representing 'no effect' is included (Higgins and Green, 2006b; Petrie and Sabin, 2000). The effect size of each individual study is presented on the axis as a block in which the size is proportional to the weight of the study, and its confidence intervals are displayed by lines extending from within the box (Higgins and Green, 2006b). A study in which the confidence intervals do not cross the line of no effect are statistically significant (Higgins and Green, 2006b). The data contributing to these point estimates are included for each study on the line corresponding with the visual representation of the data (Higgins and Green, 2006b). These include the number of patients in each intervention group, the number of events in each group for binary outcomes, point estimates and confidence intervals, and the relative weight the study contributes to the analysis (Higgins and Green, 2006b). For binary outcomes presented as OR or RR, the logarithmic scale is used to present the data visually owing to its ease of interpretation when compared to the natural scale as this allows results of the same magnitude but in different directions to be presented equidistant from the line of no effect (Galbraith, 1988; Higgins and Green, 2006a, b).

The combined effect size obtained from the meta-analysis is displayed as a diamond under the results of the individual studies and the width of the diamond expresses the precision of the result obtained (Higgins and Green, 2006b). A meta-analysis is considered to be statistically significant when the diamond does not cross the line of 'no effect' (Higgins and Green, 2006b). Additional data including the total number patients receiving each investigated intervention, numerical presentation of the combined effect and its confidence intervals and outcomes of the tests of heterogeneity are also summarised for the meta-analysis (Higgins and Green, 2006b). If subgroup analyses have been conducted the data corresponding to each subgroup is also presented in this manner (Higgins and Green, 2006b).

In situations where a meta-analysis of a planned outcome is not possible, for example to due to one or no eligible studies being located that report on this outcome, forest plots are not presented (Higgins and Green, 2006b).

2.5.2 Models of Meta-analysis

Meta-analyses are performed using one of two statistical models: fixed or random effects. The decision as to which is most appropriate depends on the context to which the meta-analysis is applied.

2.5.2.1 Fixed Effect Model of Meta-analysis

The fixed effect model of meta-analysis is underpinned by the assumption that there is one true effect size shared by all the studies included in the meta-analysis, and as such, only within-study variation is present (Borenstein *et al*., 2007; Greenland, 1994; Sutton and Higgins, 2008). For this reason the observed combined effect is understood to be distributed around the true effect size, in which the variance is largely dependent on the sample size of each study included (Borenstein *et al*., 2007). The expression of the fixed effect model may be described as

$$T_i = \theta + e_i, \tag{2.1}$$

where T_i is the observed effect, θ is μ for $i = 1,2,3 \dots k$, and e_i is the error within studies (Brockwell and Gordon, 2001; Huedo-Medina *et al*., 2006).

The assumption under which the fixed effect model operates may be conceptualised as all studies drawing their data from one homogenous population (Borenstein *et al*., 2007). As such, there is one combined effect to be determined and one level of error to be accounted for, i.e. random variation occurring within studies due to sampling error (Borenstein *et al*., 2007). As a result of this assumption, the assignment of weight to the information provided by each study through the use of the inverse variance is roughly proportional to the sample size (Borenstein *et al*., 2007). In practice, this results in the larger studies having the greatest influence within the analysis, and smaller studies having considerably less effect on the combined estimate relative to the large studies (Borenstein *et al*., 2007). The weighting assigned to the *j*th study variable using a fixed effect model can be described as

$$w_j = \frac{1}{v_j}, \tag{2.2}$$

where w_j is the weighting attributed to study variable j and v_j is the within-study variance (Borenstein *et al*., 2007).

2.5.2.2 Random Effects Model of Meta-analysis

In contrast to the fixed effect model, the random effects model allows for a range of normally distributed true effect sizes within the studies included in the meta-analysis (Borenstein *et al*., 2007; Brockwell and Gordon, 2001; Greenland, 1994; Sutton and Higgins, 2008). It acknowledges that different studies may yield similar results in which the combined estimates obtained will represent a mean of true effects of the populations studied (Borenstein *et al*., 2007). In addition to within-study variation, the assumption that each study represents a slightly different population adds an additional layer of sampling error, i.e. between-study variation (Borenstein *et al*., 2007; Brockwell and Gordon, 2001; Greenland, 1994; Sutton and Higgins, 2008). Although the between-study variance is unknown it is estimated using a method described by DerSimonian and Laird (1986) for use within the random effects model. Between-study variation is commonly denoted as τ^2 or ϵ (Borenstein *et al*., 2007; Greenland, 1994).

Between and within study variances are assumed to be independent (Brockwell and Gordon, 2001). In this sense both fixed and random effects models utilise a common structural function of measured study characteristics, however, the random effects model differs through an adjustment for unmeasured differences and biases present between studies (Greenland, 1994). As the between-study differences are the only difference between the models, comparable results will be produced using either model in a meta-analysis in which no residual differences between studies are present (Greenland, 1994). The random effects model of meta-analysis is defined in Equations 3.8 in the 'Materials and Methods' in Chapter 3.

Weights in the random effects model are also assigned using the inverse variance method, however, between-study variance is also incorporated into the value in (Borenstein *et al*., 2007): the method of assigning this weighting is defined in Equations 3.9 in the 'Materials and Methods' in Chapter 3. The result of this is that smaller studies are weighted more heavily than they would be using a fixed effect model, and larger studies do not influence the combined estimates as strongly (Borenstein *et al*., 2007). In this sense the random effects model may be described as a variation on the fixed effect model that incorporates less precision to factor in additional variation beyond that of sampling error. That is, in the presence of heterogeneity, a random effects model will yield wider confidence intervals and more conservative estimates of statistical significance than would be attained through a fixed effect model (Brockwell and Gordon, 2001; Higgins and Green, 2006a). Conversely the fixed effect model may be described in the context of the random effects model where the random effects variance equals zero (Brockwell and Gordon, 2001). Random effects models have been shown to be especially effective for use in groups of studies where overdispersion is present (Olkin, 1994).

However, limitations of the random effects model may result in misleading meta-analysis interpretations. There is potential for the random effects model to be applied as a remedy for between-study heterogeneity, thus removing the need for further consideration or investigation of these differences (Greenland, 1994): this is a misuse of a model that has been designed to only compensate for unexplainable variation (Higgins and Green, 2006a). Exploration of between-study differences is a primary value of the meta-analysis technique and consideration of the sources or predictors of heterogeneity is a means to better understand the data being investigated (Greenland, 1994; Higgins and Green, 2006c). It should also be noted that in cases when limited information is available (such as a small study sample), random effects models poorly estimate between-study variance (Sutton and Higgins, 2008). A further criticism of the random effects model is the traditional choice of applying a normal distribution (Higgins and Green, 2006a; Sutton and Higgins, 2008). Goodness-of-fit modelling is difficult to investigate in meta-analyses with small study numbers, so the validity of such assumptions is questionable (Higgins and Green, 2006a; Sutton and Higgins, 2008).

Furthermore, the effect on analysis outcomes of assuming that a normal distribution applies is not known (Higgins and Green, 2006a). Another limitation of the random effects model when applied to small numbers of studies or in studies reporting rare events is that it poorly estimates the width of distribution of treatment effects (Higgins and Green, 2006a). Finally, random effects meta-analysis methods are prone to exacerbating publication bias, as smaller studies involving less robust methodological quality and bias weighted more heavily than would occur in the fixed effect model (Greenland, 1994; Higgins and Green, 2006a).

2.5.2.3 Selection of Model for Meta-analysis

Model selection for meta-analysis should be informed by the context of the data being studied (Borenstein *et al*., 2007). In clinical practice the assumptions of the fixed effect model are rarely plausible (Borenstein *et al*., 2007). Differences in patient demographics, health care practitioner skills and practices, hospital foodservice provision, service availability and implementation of differing hospital policies are just a few of the many factors that render the assumptions of the fixed effect model void when applied to meta-analyses evaluating therapeutic or clinical interventions. Therefore, logic would suggest the random effects model is more appropriate for meta-analysis in these settings (Borenstein *et al*., 2007).

An alternative theory for model selection is to base the decision on the detection of heterogeneity through the use of the Q statistic or I^2 Index. Some authors advocate that the presence of heterogeneity mandates the use of a random effects model to account for within- and between-study variability, while its absence suggests the use of a fixed effect model (Brockwell and Gordon, 2001; Huedo-Medina *et al*., 2006). However, due to the low power of the tests for heterogeneity between-study variation may remain undetected (Borenstein *et al*., 2007; Brockwell and Gordon, 2001). This may in turn result in an inappropriate application of the fixed effect model to substantially dispersed data (Borenstein *et al*., 2007). Conversely, the application of a random effects model in a data set with less than expected dispersion will not affect the outcomes obtained: the random effects model will function in the same manner as the fixed effect model (Borenstein *et al*., 2007). For these reasons the random effects model is recommended for application to meta-analyses of clinical trials, even in cases where tests of heterogeneity do not reject the null hypothesis (Borenstein *et al*., 2007; Brockwell and Gordon, 2001; Higgins and Green, 2006a).

2.5.3 Heterogeneity

Heterogeneity is the variation occurring between studies and may arise from issues such as differences within the studied population, interventions imposed, exposures being studied, methodological design and outcomes obtained (Sutton and Higgins, 2008). Although some degree of heterogeneity is inevitable in a meta-analysis due to the realities of clinical practice (Ioannidis and Lau, 1998; Sauerland and Seiler, 2005), the degree of between-study heterogeneity present determines the quality and legitimacy of the results obtained (Ng *et al*., 2006). Detection of heterogeneity within and between the studies included in a meta-analysis is an essential step in meta-analytical procedures as it has implications for proceeding with the analysis and interpretation of obtained results (Ng *et al*., 2006; Sauerland and Seiler, 2005). The Q test and I^2 Index are described in the 'Materials and Methods' section in Chapter 3. A comparison of each assessment of heterogeneity is outlined below.

2.5.3.1 Assessment of Heterogeneity – Q Statistic

Heterogeneity in meta-analysis has traditionally been assessed with a Q test (Huedo-Medina *et al*., 2006; Ioannidis *et al*., 2007). While the Q statistic is useful to detect heterogeneity and inform on the degree of its statistical significance, it is unable to describe the extent of the presence of true heterogeneity (Huedo-Medina *et al*., 2006).

2.5.3.2 Assessment of Heterogeneity – I^2 Index

An alternative method for assessing heterogeneity is the I^2 index used in conjunction with its confidence intervals (Higgins and Thompson, 2002). The I^2 index presents as a percentage the total variability that can be attributed to true heterogeneity within a set of effect sizes (Huedo-Medina *et al*., 2006). Therefore an I^2 index equalling 0% suggests no between-study variability occurring within the analysis and that all variation observed is a result of sampling error. Conversely, the degree to which an I^2 index approaches 100% suggests the extent to which the observed variation can be attributed to between-study variability rather than sampling error. Differing classifications for interpreting the degree of variability described by the I^2 index are found in the literature however an I^2 index of 50% or more can be interpreted as describing significant heterogeneity (Higgins and Green, 2006a; Huedo-Medina *et al*., 2006).

In this way the I^2 index is preferable to the Q statistic as it can quantify the extent to which between-study variability is present (Huedo-Medina *et al*., 2006). When the I^2 index is used in conjunction with its confidence intervals it also provides a measure of statistical significance of the percentage provided, i.e. a confidence interval that includes 0% supports the null hypothesis of homogeneity between studies, while a confidence interval that does not cover 0% rejects the null hypothesis and supports the presence of heterogeneity (Huedo-Medina *et al*., 2006). For this reason the I^2 index has been proposed as a superior method for assessing heterogeneity in meta-analyses as it provides the same function as the Q statistic while providing an additional layer of information (Huedo-Medina *et al*., 2006).

The use of the I^2 index also has limitations. Firstly, despite its advantages over the Q statistic, the I^2 index does not overcome all of Q's limitations (Huedo-Medina *et al*., 2006; Ioannidis *et al*., 2007). Both methods have low statistical power to detect heterogeneity when study numbers are small and may be oversensitive to detect heterogeneity when large study numbers are present (Huedo-Medina *et al*., 2006). Secondly, when reported in the absence of its 95% confidence intervals, the I^2 index may be open to misinterpretation about the degree of heterogeneity present (Ioannidis *et al*., 2007). This is because an I^2 estimated at 0% may still have wide 95% confidence intervals and an upper 95% confidence interval that reflects substantial heterogeneity may be an indication that considerable heterogeneity is present (Ioannidis *et al*., 2007). For these reasons it is recommended that the I^2 index always be reported with its 95% confidence intervals (Ioannidis *et al*., 2007).

2.5.4 Publication Bias

The vulnerability of meta-analysis to publication bias is a commonly expressed concern and one of the major criticisms of the technique as the validity of a meta-analysis is reliant on a thorough representation of eligible studies being located (Higgins and Green, 2006a; Ng *et al*., 2006; Sutton and Higgins, 2008; Tang and Liu, 2000). The selective publication of studies, such as those with statistically significant results and those from large, multicenter trials in preference to smaller studies or those demonstrating little treatment effect, is well recognised within the literature (Duval and Tweedie, 2000; Egger and Smith, 1998; Sauerland and Seiler, 2005). Studies with statistically significant results are three times more likely to be published and in a timelier fashion than those that do not report a significant treatment effect (Egger and Smith, 1998). Studies sponsored by pharmaceutical companies are less likely to be published than those funded by government or other organisations, and multi-centred studies are more likely to be published than single centre studies (Dickersin *et al*., 1992; Easterbrook *et al*., 1991; Stern and Simes, 1997). These realities of publishing practices may result in pooled effect sizes obtained from studies exclusively located from the published scientific literature demonstrating a more significant result in terms of the magnitude of harm or benefit of an intervention than in actuality (Duval and Tweedie, 2000; Sauerland and Seiler, 2005): this has serious implications for application of meta-analysis recommendations to clinical practice.

There are several methods available for the investigation of publication bias. These may be broadly categorised as those developed to assess for the presence of publication bias, to examine of the impact of publication bias, to adjust for the assumed presence of publication bias and to predict the number of 'missing' studies and thus the likelihood of publication bias being present (Rothstein, 2008). These are discussed in sections 2.5.4.1 to 2.5.4.5.

2.5.4.1 Assessment of Publication Bias – Funnel Plots

Funnel plots are the traditional and widely used method for detecting publication bias in meta-analyses (Deeks *et al*., 2005; Egger and Smith, 1998; Higgins and Green, 2006a; Ng *et al*., 2006; Sauerland and Seiler, 2005; Sterne and Egger, 2001; Sutton and Higgins, 2008). Funnel plots are a form of scatter plot in which the treatment effect for individual studies are plotted against a measure of study precision such as standard error, the inverse standard error (precision), study size or variance (Egger and Smith, 1998; Rothstein, 2008; Sterne and Egger, 2001). A funnel plot of a meta-analysis free of publication bias is symmetrical, with the points on the scatter plot forming an inverted funnel shape around an overall treatment effect (Higgins and Green, 2006a; Ng *et al*., 2006; Sterne and Egger, 2001; Tang and Liu, 2000). The expected inverted funnel shape is attributable to the effect of increasing precision with increasing study size and the expectation that larger more highly powered studies will be outnumbered by smaller studies showing differing outcomes (Rothstein, 2008; Sterne and Egger, 2001). However, the interpretation of symmetry equating to absence and asymmetry indicating presence of publication bias has been suggested to be misleading and too simplistic owing to the number of other factors that can affect the shape and symmetry of funnel plots (Higgins and Green, 2006a; Sterne and Egger, 2001; Tang and Liu, 2000).

Firstly, Sterne & Egger (2001) demonstrated differences in shapes of funnel plots when different metrics are used for binary outcomes. The conventional funnel shape only applies when log ORs are plotted against standard error, while parabola and sharply curved lines are seen to be more appropriate descriptors of desired, bias-free plot shapes when 95% confidence intervals were applied to variance or inverse measures of standard error or variance, respectively. They also demonstrated that functions of sample size are unable to be assessed for 95% confidence intervals so should not be used in the construction of a funnel plot (Sterne and Egger, 2001). Furthermore, symmetric but not funnel-shaped funnel plots may conceal the visual detection of publication bias (The Cochrane Collaboration, 2002). Secondly, the presence of true heterogeneity or the overestimation of treatment effects due to flawed research methodology also impact on the shape and direction of the funnel plot (Sterne and Egger, 2001; Tang and Liu, 2000). Thirdly, the model of meta-analysis applied has the potential to impact on the detection of publication bias. As random effects models give relatively higher weighting to smaller studies than the fixed effect model, the magnitude of bias is increased if publication bias is present in meta-analyses in which the random effects model is applied (Greenland, 1994; Sterne and Egger, 2001). Finally, the assessment of a funnel plot symmetry or lack of it is generally conducted visually, and therefore is a subjective evaluation (Duval and Tweedie, 2000; Egger *et al*., 1997b; Higgins and Green, 2006a). Nevertheless, funnel plots continue to be promoted for assessment of publication bias (Higgins and Green, 2006a), and appear to have merit as a method of data exploration (Sutton and Higgins, 2008).

2.5.4.2 Assessment of Publication Bias - Statistical Tests

A number of statistical tests have been developed to assess for the presence of publication bias in an attempt to overcome the limitations of the visual assessment of funnel plots.

Begg and Mazumdar (1994) apply a non-parametric rank correlation test based on standardised effects sizes to the assessment of publication bias. This method is based on Kendall's rank correlation co-efficient and utilises the correlation between the standardised effect size and the variance anticipated between these two measures to detect publication bias (Begg and Mazumdar, 1994). A strong correlation suggests bias is present, while a correlation of zero indicates the absence of bias (Rothstein, 2008). However, due to the limitations of this method the absence of a statistically significant correlation cannot exclude the presence of bias (Rothstein, 2008). As it possesses limited power to assess for bias in meta-analyses with less than 25 included studies and in two-sided selection processes in which treatment effects may not differ greatly between control and intervention groups, this remains a major limitation to its application to medical meta-analyses in which these characteristics are common (Begg and Mazumdar, 1994; Rothstein, 2008). Furthermore when this test is applied to meta-analyses where very large effect sizes are observed, where included studies have comparable sample sizes, or where studies do not exceed a medium sample size, Type I errors have been shown to be exaggerated (Sterne *et al*., 2000).

As an alternative to the rank correlation approach, Egger *et al* (1997b) suggest the use of linear regression on the natural logarithm scale of the OR as a more objective assessment of the funnel plot asymmetry. This parametric test uses the regression equation

$$\mathbf{SND} = a + b \times \mathbf{precision} \tag{2.3}$$

in which SND is the Standard Normal Deviate (OR divided by its standard error), *a* is the y intercept of the SND, and *b* is the slope of the regression line (Egger *et al*., 1997b). Funnel plot symmetry is seen when the regression line intercepts the y axis at zero, while the degree of asymmetry is determined by the extent of deviation from the zero point (Egger *et al*., 1997b). Further interpretation of the *a* assists in understanding of the source of discrepancy; results in negative values suggest smaller studies show more favourable treatment effects than larger studies, while more positive values indicate more beneficial results have been reported in larger studies (Egger *et al*., 1997b). However, there are several limitations of this alternative method.

A 90% confidence interval is recommended to be applied in recognition of its limited statistical power to detect heterogeneity when a small number of studies (k<10) are present (Egger *et al*., 1997b; Rothstein, 2008). While a large proportion of Type I errors are recognised with this method in certain situations, such as when applied to binary outcomes, the power for this test is greater than for the rank correlation method (Rothstein, 2008; Sutton and Higgins, 2008). While both these methods investigate the presence of publication bias, they are unable to assess the effect of absence of bias on the results (Rothstein, 2008).

2.5.4.3 Assessment of Impact of Publication Bias – Cumulative Meta-analysis

The application of cumulative meta-analysis has the potential to be used as a method for assessing the impact of publication bias (Rothstein, 2008). In this method the included studies are ordered from largest to smallest sample sizes and the meta-analysis is repeated as the next smallest study is included in the analysis. Publication bias is considered to be absent when the smaller studies do not affect the point estimate (Rothstein, 2008).

2.5.4.4 Adjustment for Publication Bias – 'Trim and Fill' Approach

The non-parametric 'Trim and Fill' approach presented by Duval and Tweedie (2000) is a procedure that 'trims' the study data from the symmetric core of the funnel plot to obtain an estimate of the true mean, then adjusts this and the variance estimate with consideration of the data from the asymmetric part of the plot. This information is then used to generate pseudo-data representing studies assumed to have remained unpublished, which are then superimposed onto the funnel plot (Duval and Tweedie, 2000). An adjusted point estimate and variance using the actual and pseudo study data from the 'filled' funnel plot is then generated (Rothstein, 2008). The results of the adjusted and actual meta-analysis are compared for differences that project the impact of missing studies (Rothstein, 2008).

While the 'Trim and Fill' method offers an additional option for sensitivity analysis, there are a number of limitations with its application. Firstly, it attributes all asymmetry seen in a meta-analysis to publication bias (Rothstein, 2008). This assumption is difficult to justify in view of the other factors that may result in funnel plot asymmetry and that adjusting for 'missing' studies under these circumstances will provide misleading results (Rothstein, 2008). Secondly, it calculates the number of missing studies based on a predictable pattern that it assumes publication bias to follow (Rothstein, 2008). Thirdly, assumptions consistent with the fixed effect model of meta-analysis are made for the 'Trim and Fill' method, i.e. that sampling error is primarily responsible for the variance within a meta-analysis (Rothstein, 2008).

Consequently it has been shown to poorly detect the presence of between-study heterogeneity, adjusting for bias irrespective of whether it is present (Terrin *et al*., 2003).

2.5.4.5 Prediction of the Number of Missing Studies

Another strategy to correct for publication bias is the 'Failsafe N' procedure. This method was the first to be developed to deal with the issue of publication bias and makes an estimation of the number of similar sized null studies that would be necessary to eliminate the significant effect seen on an asymmetric funnel plot (Rothstein, 2008; The Cochrane Collaboration, 2002). Under this method, the estimation of only a small number of null studies to elicit a change to funnel plot shape may lend further support to the suspicion of the presence of publication bias (The Cochrane Collaboration, 2002). Failsafe N is limited in its application for a number of reasons. These include its applicability to only the fixed effect model of meta-analysis, and its development for early meta-analyses where *P*-values rather the effect sizes were calculated for combined analysis (Rothstein, 2008). As a result, its premise relates to statistical significance rather than the practical or theoretical application (Rothstein, 2008). In effect, it questions the number of studies to affect the statistical significance of the outcome, not the number required to have no effect of the estimate of effect size (Rothstein, 2008).

Probability modelling for the likelihood of certain study results being published or remaining unpublished can also be performed in an attempt to determine the likelihood of publication bias affecting meta-analysis results (The Cochrane Collaboration, 2002).

2.5.4.6 Cautions Regarding the Application of Data from Assessments of Publication Bias

Assessment for the presence of publication bias (along with other biases) should be conducted prior to embarking on a meta-analysis in an attempt to gauge the appropriateness of continuing (Begg and Mazumdar, 1994). Failure to do so may inadvertently result in a violation of the general principles of meta-analysis that states studies included have to be 'combinable' – the presence of substantial bias or true heterogeneity would suggest it is inappropriate to pool such studies (Egger *et al*., 1997a; Ng *et al*., 2006). In this context the wisdom of applying methods to compensate for publication bias in isolation of its function as a sensitivity analysis has been questioned, especially when the implications of applying the outcomes of meta-analysis to clinical practice are considered (Sutton and Higgins, 2008). Ultimately it should be remembered that assessments for publication bias are a form of sensitivity analysis and the methods currently available are unable to provide definitive answers regarding the presence of publication bias or its sources (The Cochrane Collaboration, 2002).

2.5.5 Other Sources of Bias in Meta-analysis

Pooling results from multiple studies retrospectively will inevitably result in pooling the biases included in each individual study and this remains a principal criticism of meta-analysis (Moher *et al*., 1998; Ng *et al*., 2006). Common biases such as location and methodological quality are outlined in the following subsections.

2.5.5.1 Location Bias

Inaccessibility of relevant "fugitive" literature such as dissertations, PhD chapters or unpublished trials and additional data required from authors of published reports may result in a biased meta-analysis (Egger and Smith, 1998; Ng *et al*., 2006). English language bias is introduced by limiting included studies to English language publications as relevant studies may be missed if they have been reported exclusively in languages other than English or in local non-English publications (Egger and Smith, 1998; Ng *et al*., 2006; Sauerland and Seiler, 2005). Positive findings are recognised as being more likely to be submitted to and published in English language publications (Egger and Smith, 1998; Ng *et al*., 2006). Studies published in journals not indexed on major electronic databases such as Medline or Embase are unlikely to be identified through literature searches and so introduce database bias (Egger and Smith, 1998; Ng *et al*., 2006). Due to the underrepresentation of publications from developing countries in these databases, relevant studies from emerging research centres in locations such as India and China may be missed (Egger and Smith, 1998). The use of reference lists as a means of locating articles may introduce citation bias, as frequently cited studies are more likely to be located using this method (Egger and Smith, 1998). Multiple publication bias resulting from several publications being produced following large, positive or multi-centre studies may unintentionally duplicate data included or increase the likelihood of the study's results being included in the meta-analysis (Egger and Smith, 1998; Ng *et al*., 2006). It may also be possible for investigators to inadvertently introduce bias when formulating the inclusion criteria for the meta-analysis if they are well versed in the area being investigated, and thus may be familiar with many of the studies available and their results (Egger and Smith, 1998). Similarly undertaking a meta-analysis with a preconceived outcome, theory or hypothesis in mind may bias the conclusions drawn by overlooking equally plausible alternate conclusions from the data available (Olkin, 1994).

2.5.5.2 Poor Methodological Quality

While methodological quality is regularly investigated in meta-analyses as a possible explanation for heterogeneity or discrepancies noted between study outcomes, these methods have received criticism for being too arbitrary and subjective while retaining the appearance of objectivity (Greenland, 1994). Concerns exist that simple methodological scores may conceal important between-study variation (Greenland, 1994).

Several authors have demonstrated an amplification of treatment effect by 30 to 50% when estimates obtained from studies of low methodological quality are compared with studies of high methodological quality (Moher *et al*., 1998; Sauerland and Seiler, 2005; Schulz *et al*., 1995). Others have failed to replicate these results (Balk *et al*., 2002; Emerson *et al*., 1990). Possible reasons for the differences in these study outcomes lie in variation of definitions and interpretation of methodological quality, choice of quality score, medical speciality the evaluation was applied to, the statistical power of the empirical assessments undertaken or the studies or meta-analyses included in the assessments (Balk *et al*., 2002). Furthermore, it is often difficult to differentiate studies that are actually of low methodological quality from those that do not report their methods thoroughly (Balk *et al*., 2002; Higgins and Green, 2006a).

Due to the differing outcomes of these investigations, there are contradictory recommendations for dealing with the issue of methodological quality of the studies included in a meta-analysis. Some authors recognise the potential for low quality studies to influence the results obtained and advocate for *a priori* analyses on methodological quality to be conducted (Ng *et al*., 2006; Sauerland and Seiler, 2005). Other sources recommend against the routine use of quality scores that oversimplify complex data, but suggest sensitivity analyses incorporating aspects of the quality-related study characteristics such as randomisation and blinding (Greenland, 1994; Higgins and Green, 2006a; Olkin, 1994).

2.5.6 Sensitivity Analysis for Bias Exploration

Sensitivity analyses are undertaken to explore sources of bias or effect modifiers that are suspected to be present among the included studies (Ng *et al*., 2006; Sauerland and Seiler, 2005). They are performed by altering features of the initial analysis with a view to assessing the robustness of obtained results when different aspects of the analysis are altered (Higgins and Green, 2008). Examples of sensitivity analyses may include exclusion of studies on the basis of methodological quality or sample size; analysis with both random and fixed effect statistical models; or inclusion of studies in which unclarified or ambiguous reporting resulted in earlier exclusion (Higgins and Green, 2008; Ng *et al*., 2006; Olkin, 1994). Methods for detection of publication bias are a specific form for sensitivity analysis (Sutton and Higgins, 2008). Results obtained from sensitivity analyses are compared with the primary analysis and assessed for consistency, i.e. in a meta-analysis free of bias the results of a sensitivity analysis should not differ significantly from the pooled results of the primary analysis (Ng *et al*., 2006). Under these circumstances the primary analysis' results may be accepted with a greater degree of confidence (Higgins and Green, 2008). Conversely, when the analysis reveals aspects that greatly modify the results obtained, the overall results of the primary analysis must be interpreted with caution (Higgins and Green, 2008).

The decision to perform a sensitivity analysis may be made during the planning stages of a meta-analysis, however it is often the decisions and uncertainties identified while undertaking the review that highlight the need for these investigations (Higgins and Green, 2008). Often multiple sensitivity analyses are utilised to explore the data (Olkin, 1994).

Sensitivity analyses are distinct from subgroup analyses in several ways. Firstly, while sensitivity analyses compute a combined effect for the altered analysis, they do not attempt to obtain a combined effect size for each subgroup as occurs with subgroup analysis (Higgins and Green, 2008). Secondly, only informal comparisons are made between the results of a sensitivity analysis and primary analysis while formal assessments based on the resulting statistics are made within a subgroup analysis (Higgins and Green, 2008). These distinctions may become blurred however when subgroup analyses are utilised as a predefined sensitivity analysis where more formal comparisons are made for the purpose of generating hypotheses or investigating anticipated differences within the pooled data (Sauerland and Seiler, 2005).

2.5.7 Subgroup Analyses

Subgroup analyses obtained from a larger meta-analysis have the potential of providing information on patient groups with specific characteristics and may be useful as an exploratory method. However, they potentially introduce non-randomised biases into the analysis and should be interpreted with caution (Higgins and Green, 2006a). As such, they cannot conclusively confirm relationships between outcomes and the subgroup population and may provide erroneous results when conducted as a post hoc analysis (Davey Smith *et al*., 1997; Olkin, 1994). For this reason, subgroup analyses should be planned prospectively to minimise the effect of bias and should have at a minimum of ten studies per subgroup available to justify the analysis (Higgins and Green, 2006a).

2.5.8 Application of Meta-analysis Results

Results of meta-analyses provide a summary of the treatment effects of a particular intervention from a number of studies, however they do not provide information about which individual patients the intervention may benefit in clinical practice (Smith and Egger, 1998). As clinical practice is primarily interested in care of the individual, the inability of meta-analysis techniques to assist with the elucidation of causal relationships implicit in their data makes it difficult to apply the results of group outcomes to individual behaviour (Olkin, 1994).

Nevertheless, a well conducted meta-analysis is a valuable tool for clinical sciences such as surgery and nutrition when due caution in interpretation of results is observed (Egger and Smith, 1997). As demonstrated in Figure 2.1, meta-analysis performed as part of a systematic review is considered to represent the highest level of evidence in conceptualisations of evidence-based practice (Evans, 2003; National Health and Medical Council, 2005).

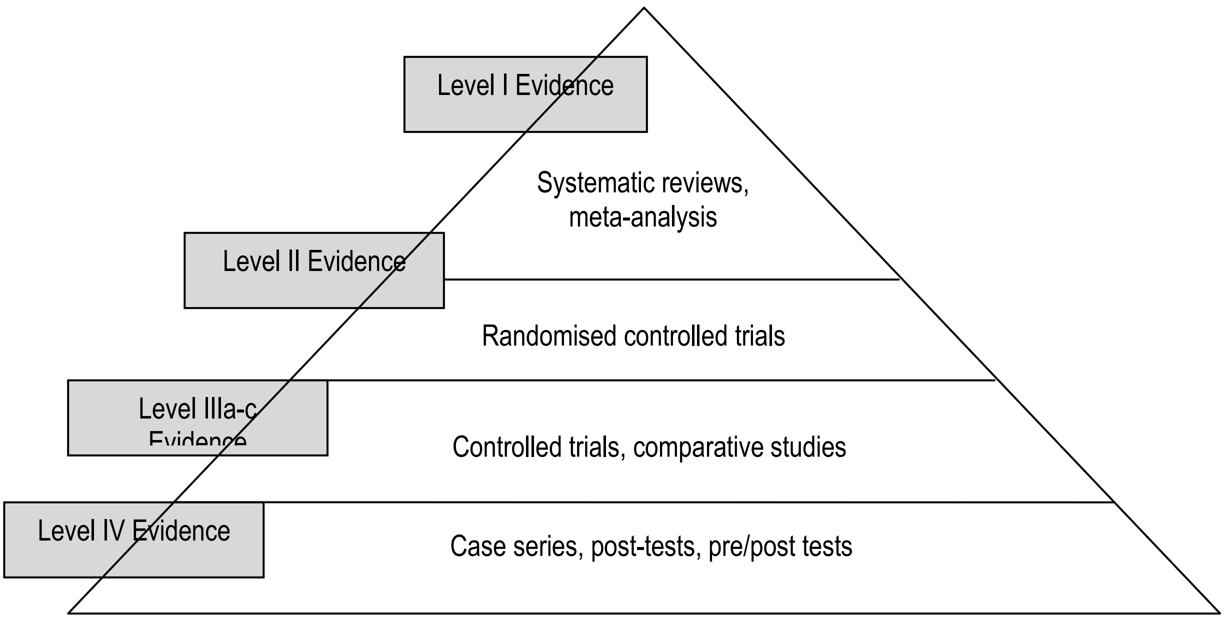

Figure 2.1 Hierarchy of Evidence underpinning the concept of Evidence-Based Practice. Adapted from National Health and Medical Research Council (2005).

2.5.9 Previous Meta-analyses on Early Feeding

Three meta-analyses exist in the literature investigating the outcomes of feeding within 24-hours following elective gastrointestinal surgery compared with traditional nil-by-mouth practices (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). The first was published in 2001 and includes 11 studies, while the 2006 and 2008 meta-analyses are updates of the original 2001 publication (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). The major changes to the updated papers are the inclusion of a further two studies (Mulrooney *et al*., 2004; Smedley *et al*., 2004) and the reporting of outcomes using a random effects model of meta-analysis in addition to the fixed effect model in the 2008 paper (Andersen *et al*., 2006; Lewis *et al*., 2008). All meta-analyses sought RCTs that utilised the gastrointestinal tract for nutritional provision (orally or via feeding tube) within 24-hours following elective gastrointestinal surgery, and include studies that range from 1979 to 2004 (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). Colorectal surgery accounted for the majority (71%) of the study population that included 837 (Lewis *et al*., 2001) to 1173 patients (Andersen *et al*., 2006; Lewis *et al*., 2008).

Lewis *et al* (2001) demonstrated a significant reduction in all postoperative infections with early feeding compared with traditional practice (RR 0.76; 95% Confidence Interval (CI), 0.54-0.98; *p*=0.036), however, this outcome was not reported in subsequent publications. When rates of infection at specific locations were analysed, trends favouring early feeding for reduction in development of wound infection (RR 0.71; CI 0.44, 1.17), pneumonia (RR 0.73; CI 0.33, 1.59) and intra-abdominal abscesses (RR 0.87; CI 0.31, 2.42) were observed (Lewis *et al*., 2001). Comparable results were reported in the 2006 and 2008 publications (Andersen *et al*., 2006; Lewis *et al*., 2008). A significant reduction in postoperative mortality was associated with early feeding in the 2006 and 2008 meta-analyses (RR 0.41; CI 0.18, 0.93; *p*=0.03), with little difference seen when a random effects model of meta-analysis was applied (RR 0.42; CI 0.18, 0.96; *p*=0.03) (Andersen *et al*., 2006; Lewis *et al*., 2008). All meta-analyses report significant reductions in LOS with early feeding interventions (WMD between -0.84 and -0.89; CI -1.33, -0.36; *p*=0.001, using fixed effect model, and CI -1.58, -0.20 using random effects model, respectively), though with some heterogeneity detected (χ^2 16.2 to 18.88, *p*=0.09 in both analyses) (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). Similarly, a significant 25% increase in the incidence of postoperative vomiting was associated with early feeding interventions in all analyses (RR 1.27; CI 1.01, 1.61; *p*=0.04 in fixed effect and RR 1.23; CI 0.97, 1.55 in random effects model) (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). Trends favouring early feeding with regards to rates of anastomotic dehiscence were also seen in all analyses (RR 0.53; CI 0.26, 1.08 to RR 0.62; CI 0.36, 1.32), however these were not statistically significant (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001).

2.6 Development of Perioperative Practices – Reducing Surgical Stress

It is important to consider the practice of early postoperative in the context of larger changes occurring within surgical practice over the last 50 years in which a principal goal has become the reduction of physiological stress following surgery (Wilmore, 2002).

2.6.1 Physiology of Surgical Stress

The injury resulting from surgery sets in motion a cascade of neuroendocrine and inflammatory reactions that mediate a metabolic response to traumatic stress first described by Sir David Cuthbertson in the 1920s (Wilmore, 2002). Effects of trauma on the sympathetic nervous system stimulate the secretion of cortisol, catecholamines and glucagon which promote catabolism of protein stores to mobilise amino acids for wound healing and synthesis of acute phase response and immune proteins (Brunicardi, 2005; Sobotka *et al*., 2004). Hyperglycaemia is promoted to fuel the anaerobic energy metabolism utilised by wounds, ischaemic tissues, macrophages and fibroblasts through these hormones' effect on insulin resistance, gluconeogenesis, reduced glucose oxidation by muscles and reduced glucose storage (Brunicardi, 2005; Grimble, 2008). Higher than normal blood glucose levels also function to provide an osmotic gradient required to drive glucose into the poorly perfused, damaged cells (Champe and Harvey, 1994). The net effect of these changes is to re-establish homeostasis post injury (Correia and da Silva, 2004) and to redistribute substrate utilisation away from roles that are non-essential during times of metabolic stress in preference of tasks that are required for survival such as maintaining homeostasis, vital organ function and wound healing (Sobotka *et al*., 2004). The magnitude and duration of these stress-related metabolic changes appear to be proportional to the degree of injury sustained (Brunicardi, 2005; Correia and da Silva, 2004).

These metabolic changes exist to facilitate healing and recovery but are achieved at a high cost in terms of skeletal and visceral body mass losses that are catabolised in order to allow gluconeogenesis pathways to function (Champe and Harvey, 1994). In the short term or for mild stress, the body can absorb and recover from these losses (Correia and da Silva, 2004).

However in the field of modern medicine patients may be maintained in this state for weeks or months through advances in critical and surgical care, though they lack the evolutionary mechanisms to survive a prolonged stress response (Correia and da Silva, 2004). For these reasons the benefits of reducing the stress response in elective surgical patients has the potential to reduce the risk of postoperative complications and organ dysfunction, thus facilitating recovery (Kehlet and Wilmore, 2008).

2.6.2 Role of Nutrition in Reducing Surgical Stress Response

There are several means by which nutrition may facilitate the reduction of the stress response following surgery: these are outlined in sections 2.6.2.1 to 2.6.2.3.

2.6.2.1 Proposed Physiological Mechanisms by Which Nutrition May Reduce Surgical Stress

Enteral nutrition has been theorised to play a role in down-regulating the metabolic cascade commenced with the onset of physiological stress such as surgery or physical trauma (Rowlands and Gardiner, 1998; Sobotka *et al*., 2004). The most commonly suggested mechanism for this action is enteral nutrition's role in maintaining the integrity of the gut mucosa and thus gut barrier function (Deitch, 2002; Wischmeyer, 2005). This is thought to prevent bacterial translocation from the gastrointestinal tract into the bloodstream and microbial contamination of distant organs, which may subsequently result in organ dysfunction (Deitch, 2002; Wischmeyer, 2005). Further research into the physiology of this process suggests that cytokines and other inflammatory proteins are produced by the gut-associated lymphoid tissue [GALT] in enterocytes when they are exposed to bacteria following the failure of gut-barrier function allowing these products enter the bloodstream via the mesenteric lymph (De-Souza and Greene, 2005; Deitch, 2002; Rowlands and Gardiner, 1998; Wischmeyer, 2005). Thus, in situations such as trauma, surgery, shock and sepsis, the gut and GALT in their own right become "*cytokine generating organ[s] ... produc[ing] cytokines and other inflammatory mediators, which may contribute to systemic inflammatory response and multi-organ dysfunction syndrome*" (Deitch, 2002, p.242).

In particular the amino acid glutamine, which is well recognised as an important fuel source for enterocytes (Matarese and Gottschlich, 1998), has been identified for its possible role in preventing gut permeability through a variety of mechanisms (Wischmeyer, 2005). These include increasing tissue glutathione concentrations facilitating a buffering of oxidative stress, directly exerting anti-inflammatory effects, reducing nitric oxide synthetase expression, maintaining tissue metabolic function following injury and protecting against gut injury through the expression of heat shock proteins which are thought to prevent cellular death and/or injury in response to oxidative stress (Wischmeyer, 2005).

Furthermore, enteral nutrition stimulates luminal mucous production which provides a further barrier of protection against bacterial translocation (Matarese and Gottschlich, 1998; Rowlands and Gardiner, 1998). Irrespective of the mechanism/s by which the gut barrier is maintained, the trophic effects of enteral nutrition, even with less than nutritionally adequate provision, are well recognised (Martindale *et al*., 2009; Matarese and Gottschlich, 1998; Zaloga *et al*., 1992).

Another mechanism by which enteral nutrition may attenuate the metabolic stress response is through the stimulation of bile acid secretion (Matarese and Gottschlich, 1998; Rowlands and Gardiner, 1998). The acidity of bile salts function to deactivate luminal endotoxins (Matarese and Gottschlich, 1998), allowing a reduction in stimuli for GALT and its associated inflammatory responses.

2.6.2.2 Early Initiation of Nutrition

Provision of enteral nutrition soon after the onset of physiological stress such as surgery or physical trauma may reduce the magnitude of the stress response (Correia and da Silva, 2004). Animal studies (in guinea pigs) investigating the metabolic and endocrine responses to 30% body surface area full thickness burns have shown that nutritionally adequate feeding commenced within 2-hours of a thermal injury significantly reduces the circulating serum levels of cortisol and glucagon and urinary excretion of catecholamines when compared with control animals who received nutrition 24- to 72-hours post injury (Mochizuki *et al*., 1984). After two weeks of nutrition support, animals that received early feeding experienced less weight loss (5% versus 15% pre-burn weight) and had achieved a positive visceral nitrogen balance when compared with those that received delayed feeding (Mochizuki *et al*., 1984). A post-mortem examination of jejunal mucosal mass demonstrated almost 50% loss of mucosa in animals with delayed feeding but little change in those receiving early feeding (Mochizuki *et al*., 1984). This study also demonstrated that compensating for delayed feeding by providing a higher caloric intake at commencement of feeding 72-hours post injury is inferior to the outcomes achieved with early feeding (Mochizuki *et al*., 1984). Further studies have demonstrated that these benefits are uniquely conferred by provision of nutrition enterally and early parenteral nutrition provision failed to match the outcomes achieved with early gastric feeding (Saito *et al*., 1987).

Human studies in clinical settings have shown less consistent results. In a RCT conducted by Chiarelli *et al* (1990) patients with burns to 25 to 60% body surface area were randomised to receive very early nasogastric feeding (within 4-hours post injury) or conventional treatment (commencement at 48-hours). Both groups demonstrated metabolic and endocrine patterns consistent with a stress response, however, early feeding appeared to attenuate the magnitude of the stress response (Chiarelli *et al*., 1990). Those receiving early feeding demonstrated significantly lower concentrations of plasma glucagon and urinary catecholamine excretion and a greater proportion of patients achieved a positive nitrogen balance within three weeks post injury in the very early feeding group (Chiarelli *et al*., 1990). Other studies have failed to demonstrate metabolic or clinical outcomes supporting the ability of nutrition to ameliorate the hypermetabolism resulting from thermal or physical injury. It should be noted, however, that these studies did not commence early feeding until after 24-hours post injury (Eyer *et al*., 1993; Grahm *et al*., 1989; Jenkins *et al*., 1989). It is therefore possible that the timing of nutritional provision is critical to its beneficial action (Matarese and Gottschlich, 1998).

2.6.2.3 Preoperative Carbohydrate Loading

Preoperative carbohydrate loading is another strategy that may be beneficial in moderating the stress response that follows elective surgery through reducing the degree of postoperative insulin resistance experienced after fasting and in response to the release of counter-regulatory hormones and cytokines (Ljungqvist *et al*., 2000). Abandoning the traditional practice of fasting patients undergoing elective surgical procedures from midnight of the day of surgery and providing carbohydrate containing beverages taken up to 2-hours prior to induction of anaesthesia have been shown to reduce postoperative insulin resistance and to facilitate the maintenance of normal glucose control (Nygren *et al*., 1998; Soop, 2003). Other purported of benefits preoperative carbohydrate loading include earlier hospital discharge (Ljungqvist *et al*., 1998), preservation of peripheral muscle mass as evidenced by grip strength (Noblett *et al*., 2006) or arm muscle circumference (Yuill *et al*., 2005) and reduced nitrogen losses measured the third postoperative day (Soop *et al*., 2001).

2.6.3 Role of Non-nutritional Factors in Reducing Surgical Stress

In addition to nutrition, numerous other aspects of perioperative care may be utilised to attenuate the hypermetabolic responses induced by surgery. These are outlined in sections 2.6.3.1 to 2.6.3.7.

2.6.3.1 Minimally Invasive Surgery

The adoption of minimally invasive surgical procedures such as mini-laparotomy and laparoscopic techniques in preference to a full, open laparotomy reduces the size of the surgical wound (Evans *et al*., 2008; Kehlet and Wilmore, 2008). While it has been theorised that this minimises the magnitude of the stress response induced, investigations to date have failed to detect significant differences between metabolic and endocrine responses, specifically glycaemic control and nitrogen balance and the release of cortisol, catecholamines, glucagon, insulin and growth hormone respectively (Kehlet, 1999). Conversely, minimally invasive surgery has frequently been shown to reduce the magnitude of inflammatory and immune responses (as measured by C-Reactive Protein and Interleukin-1) when compared with traditional open surgical approaches (Kehlet, 1999, 2006; Kehlet and Wilmore, 2008). Conflicting findings are reported the literature (Fukushima *et al*., 1996).

These physiological benefits of minimally invasive surgery appear to translate into an improved postoperative recovery through reduction of postoperative complications, such as pain (Kehlet and Wilmore, 2008), pulmonary dysfunction, sleep disturbances, hypoxemia and development of paralytic ileus when compared with outcomes from traditional open surgical practices (Kehlet, 1999, 2006).

2.6.3.2 Anaesthetic Practice

The evolution of anaesthetic practice has also played a significant role in reducing the detrimental effects of surgical stress and the reduction of postoperative complications. An alternative to the provision of general anaesthesia is the concept of regional anaesthesia that began with George Crile's theory of 'anoci-association' in 1915 (Kehlet, 2006). This technique creates a neuraxial blockade by blocking the efferent and afferent nerve impulses around the surgical site via the administration of local anaesthetic drugs into the subarachnoid or epidural space and has been increasingly utilized as an alternative to general anaesthesia in a variety of surgical specialities since the early 1980s (Kehlet, 2006; Rodgers *et al*., 2000). Regional anaesthesia, particularly central neuraxial blockade with local anaesthetics, when used in preference to general anaesthesia has been shown to reduce the adverse metabolic responses to surgery as demonstrated by comparative reductions in circulating levels of cortisol and blood glucose (Desborough, 2000). The use of neuraxial blockade has been shown to significantly reduce mortality by 30% while reducing postoperative complications such as the development such as deep vein thrombosis, pulmonary embolism, transfusion requirements, pneumonia and respiratory distress when compared with general anaesthesia (Desborough, 2000; Rodgers *et al*., 2000). These advantages are thought to be due to the comparative reduction in the metabolic response required to deal with surgical stress, and the subsequent reduction in catabolic hormone production (Holte and Kehlet, 2002). This in turn reduces the degree of insulin resistance, glycogenolysis, lipolysis, and protein degradation experienced following a surgical procedure: this likely to be protective to vital organs and reduce the risk of developing organ dysfunction in the postoperative course (Holte and Kehlet, 2002).

In instances when general anaesthesia is unavoidable, prudent selection of anaesthetic agents may also facilitate a reduction in the stress response. For example, morphine and midazolam have been shown to suppress cortisol release and etomidate inhibits the production of aldosterone and cortisol (Desborough, 2000). Clonidine facilitates haemodynamic stability through effecting α_2-agonists on the sympathetic nervous system however the extent of these effects appear to be dependent on the type of surgery performed (Desborough, 2000). Thus, the concomitant pharmacological actions of these anaesthetic agents may serve to beneficially modify physiological and neuroendocrine responses mounted in response to surgical stress, thereby attenuating the magnitude of the physiological response to the trauma induced during surgery.

2.6.3.3 Prevention of Intraoperative Hypothermia

Prevention of intraoperative hypothermia has also been demonstrated to be an important aspect in the reduction of surgically induced stress responses (Wilmore, 2002). Impairment of thermoregulation as a consequence of anaesthesia, in conjunction with the lowered temperature of operating theatres, exposes patients undergoing major procedures to significant cold stress that results in increased adrenal steroid and catecholamine synthesis (Sessler, 1997). A reduction of 1 to 3°C in core body temperature intraoperatively is associated with up to a three-fold increase in postoperative wound infections, increased blood loss and postoperative cardiac arrhythmias, increased catabolism, decreased collagen synthesis, coagulopathy and patient discomfort when compared to normothermic patients (Sessler, 1997). Preventing hypothermia by maintaining patients' body temperature at 36°C intraoperatively is therefore an important strategy to reducing operative stress and improving postoperative outcomes (Sessler, 1997; Wilmore, 2002). This can be achieved through a variety of practices such as use of surgical drapes to reduce cutaneous heat losses, bair huggers, forced air warming, and fluid warming (Kurz, 2008; Sessler, 1997).

2.6.3.4 Postoperative Analgesia

The management of postoperative pain is an important consideration, as the choice of analgesia has the potential to impact the postoperative clinical course. Opioid analgesics such as morphine, codeine, fentanyl, oxycodone and pethidine are associated with a number of side effects including suppressing the cough reflex and respiratory effort, reducing gastrointestinal peristalsis which may result in constipation and faecal impaction, increased nausea and vomiting, mood changes, alterations in the endocrine and autonomic nervous system, and sedation (Donohoo *et al*., 2003). Continuous postoperative epidural analgesia provides an effective solution to pain following abdominal, vascular and thoracic surgery and has been shown to reduce the development of postoperative ileus and other postoperative complications such as thromboembolisms and cardiac complications (Desborough, 2000; Holte and Kehlet, 2002). Similarly, the concept of multimodal analgesia which incorporates regional anaesthesia techniques such as continuous central neuraxial blockade, peripheral blocks and local wound perfusion with non-opioid based analgesics (such as ketamine, non-steroidal anti-inflammatory drugs, COX-2 inhibitors, and gabapentin) effectively avoids many of the symptoms experienced with opioid analgesics.

Effective postoperative analgesia thus contributes to improved postoperative recovery by facilitating the tolerance of early nutritional intake and facilitating early mobilisation while dampening the inflammatory cascade promoted by uncontrolled postoperative pain (Kehlet, 2006; Kehlet and Wilmore, 2008).

2.6.3.5 *Early Mobilisation*

Early mobilisation, which varies in definition from sitting upright out of bed, standing unassisted or walking defined distances (Browning *et al*., 2007; Denehy, 2008), is thought to play a key role in the reduction of postoperative pulmonary complications. This is achieved through promoting respiratory effort , facilitating clearance of secretions and preventing and treating conditions such as atelectasis and hypoxaemia known to be associated with prolonged assumption of a supine position (Browning *et al*., 2007; Denehy, 2008; Mackay *et al*., 2005; Harper and Lyles, 1988). Early mobilisation also assists with reducing the risk of venostasis and therefore thromobembolism and reducing the incidence of postoperative ileus (Harper and Lyles, 1988; Zonca *et al*., 2008). Although the benefits of mobilisation in the early postoperative period have not been studied in isolation from multimodal approaches (Denehy, 2008), an observational study in patients having received upper gastrointestinal surgery demonstrated a strong, statistically significant inverse correlation between the amount of time spent in an upright position during the first four postoperative days and the LOS and development of pulmonary complications (Browning *et al*., 2007). Loss of muscular strength of up to 5% per day may be associated with inactivity and prolonged bed rest (Muller, 1970). Adverse outcomes such as intracellular dehydration, loss of muscle potassium (indicative of loss of muscle mass) have been seen in studies of prolonged bed rest in healthy volunteers, while early mobilisation has been shown to facilitate renal osmolar clearance and increase urine flow (Holte *et al*., 2002). While these effects of early mobilisation may provide protection from postoperative organ dysfuntion through retaining lean body mass and optimising fluid balance, these benefits are yet to be demonstrated in a surgical population (Holte *et al*., 2002).

2.6.3.6 *Pharmacological Agents*

The employment of pharmacological agents to assist in symptom management and direct action on systemic stress responses has also been explored (Kehlet, 2006; Kehlet and Wilmore, 2008). Examples of these include prescription of beta-blockers, in an attempt to reduce the catabolic effects exerted by the sympathetic nervous system (Kehlet, 2006); insulin, to reduce inflammatory response and protein degradation (Kehlet and Wilmore, 2008); glucocorticoids, for their ability to reduce postoperative nausea, vomiting, pain and fatigue (Kehlet, 2006; Kehlet and Wilmore, 2008; Mynster *et al*., 1996); and use of anabolic agents or hormones, for their ability to reduce rehabilitation time in vulnerable patients (Kehlet and Wilmore, 2008).

2.6.3.7 *Other Aspects of Perioperative Care*

Other aspects of traditional perioperative care have also been called into question as principles of evidence-based practice have been adopted and critical evaluation of longstanding surgical practices have been undertaken. Prophylactic gastric decompression has been used routinely following abdominal surgery in the belief it reduces a number of postoperative surgical concerns including nausea, vomiting, abdominal distension, pulmonary aspiration and resulting pneumonia, duration to resumption of bowel function and protection for the wound and/or anastomosis (Nelson *et al*., 2007). However, a recent meta-analysis has demonstrated that gastric decompression confers no benefit to the postoperative course of a patient and recommends the discontinuation of the practice (Nelson *et al*., 2007). Likewise the use of surgical drains to remove excess fluid from the abdominal cavity after surgery fail to demonstrate benefit and may contribute to adverse outcomes such as enhanced inflammatory responses resulting in anastomotic dehiscence or fistula formation in when used following gastrointestinal surgery (Memon *et al*., 2002; Urbach *et al*.,1999). In contrast to the perioperative positive fluid balance resulting in overhydration, a judicious, 'goal directed' approach to perioperative fluid management has been shown to provide reductions in LOS and postoperative morbidity (Holte *et al*., 2002; Kehlet and Wilmore, 2008). Evidence also supports abandoning the use of bowel cleansing preparations prior to colonic surgery and the prolonged use of urinary catheters, both of which have been considered important aspects of surgical management in the past (Kehlet and Wilmore, 2008; Nygren *et al*., 2003).

2.7 Multimodal Perioperative Approaches – Accelerated Recovery Programs

The concept of combining a variety of these evidence-based interventions into a structured multimodal, multidisciplinary approach to perioperative care following elective surgery was first developed in the 1990s and has become known as 'Fast-Track' or 'Enhanced Recovery After Surgery [ERAS]' (Kehlet, 2008; Kehlet and Wilmore, 2008; Wind *et al*., 2006b). This model of service provision was initially developed by Kehlet and colleagues (2002) to optimise postoperative recovery for patients undergoing elective colorectal surgery (Wind *et al*., 2006b). The primary intent of the approach is to reduce avoidable postoperative surgical complications and minimise adverse postoperative outcomes which would be anticipated to lead to the secondary benefits of reduced costs associated with hospitalisation (Kehlet and Dahl, 2003; Zonca *et al*., 2008). The ERAS principles have been successfully applied to other surgical specialities including vascular, orthopaedic, endocrine, thoracic and upper gastrointestinal surgical procedures (Kehlet and Wilmore, 2008; Wind *et al*., 2006b; Zonca *et al*., 2008).

2.7.1 Elements of Accelerated Recovery Programs

Fifteen elements that comprise the accelerated recovery program for colorectal surgery have been proposed (Kehlet and Wilmore, 2002). A further two elements have been added by other authors (Anderson *et al*., 2003; Gatt *et al*., 2005).

2.7.1.1 Preoperative Elements

Preoperatively, patients are assessed with regard to anaesthetic risk factors and optimisation of co-morbidities that may affect postoperative recovery (Kehlet and Wilmore, 2002). Patients are counselled on their planned surgical procedure along with expectations for the recovery period such as anticipated analgesia management, as psychological preparation reduces hospital LOS and postoperative analgesia requirements (Egbert *et al*., 1964; Kehlet and Wilmore, 2002). Less consistently included preoperative aspects include the provision of prebiotic and probiotic preparations for one to two weeks prior to surgery included *"in an attempt to alter the composition of gastrointestinal mircoflora favourably and to enhance gut barrier function"* (Anderson *et al*., 2003, p.1502), abandonment of premedication (Basse *et al*., 2004) and bowel preparation,and preoperative carbohydrate loading up to three hours before induction of anaesthesia to reduce postoperative insulin resistance (Anderson *et al*., 2003; Gatt *et al*., 2005).

2.7.1.2 Perioperative Elements

Perioperative principles include the selection of anaesthetic agents which optimise the postoperative course through reducing nausea and vomiting, facilitating early resumption of bowel function and attenuating the endocrine-metabolic responses to surgery that accelerate catabolism (Kehlet and Dahl, 2003; Kehlet and Wilmore, 2002); use of minimally invasive surgical techniques and/or transverse incisions (Wind *et al*., 2006b) and active prevention of intraoperative hypothermia (Kehlet and Wilmore, 2008). Avoidance of surgical drains, maintenance of high perioperative oxygen concentrations (Anderson *et al*., 2003; Gatt *et al*., 2005) and use of fluid restrictions (Basse *et al*., 2004; Raue *et al*., 2004) are less uniform in their application.

2.7.1.3 Postoperative Elements

Epidural analgesia, early mobilisation, provision of nutrition within 24-hours postoperatively, non-routine use of nasogastric tubes, and avoidance of morphine-based analgesia are widely embraced as central aspects of accelerated recovery programs of their postoperative care (Wind *et al*., 2006b). The early removal of bladder catheters and use of aperients as a standard practice have been less commonly adopted (Anderson *et al*., 2003; Gatt *et al*., 2005).

2.7.2 Outcomes of Enhanced Recovery Programs

Beneficial outcomes from the implementation of multimodal perioperative approaches have been most convincingly demonstrated in colorectal surgery. Several well designed RCTs (Anderson *et al*., 2003; Delaney *et al*., 2003; Gatt *et al*., 2005; Khoo *et al*., 2007) and a systematic review (Wind *et al*., 2006b) have demonstrated reductions in LOS in the absence of adverse mortality and morbidity outcomes with the adoption of Fast-Track principles. However, other non-randomised, single-centred studies suggest that additional benefits in the form of reduced complications, financial costs, nursing resource requirements, earlier resumption of bowel function, improved muscle strength, exercise capacity, lean body mass, improved nutritional intake, decreased cardiopulmonary morbidity and reduced duration of postoperative recovery may also be attributable to the implementation of Fast-Track principles (Kehlet and Wilmore, 2002). Despite these promising outcomes and compelling results supporting the benefits of this approach particularly in colorectal surgery, the widespread implementation of this approach to perioperative care has been slow to be adopted (Kehlet, 2006; Kehlet *et al*., 2006; Kehlet and Wilmore, 2008; Zonca *et al*., 2008).

2.8 Summary

When compared with traditional nil-by-mouth postoperative nutritional management, early feeding following elective gastrointestinal surgery has been shown to be safe and may confer clinical benefit in the individual studies that have investigated these interventions. However, these clinical trials are often small and statistically underpowered to confidently promote change to practice. Meta-analysis is a statistical method that incorporates the results of comparable studies investigating an intervention, and allows the outcomes of each to be assessed as part of the whole. This increases the statistical power of the analysis and may provide stronger justification to change clinical practice. The three meta-analyses available on this topic contain major errors and therefore a further meta-analysis with greater emphasis on nutritional and statistical factors is required. Chapter 3 outlines the methodology of the meta-analysis undertaken to achieve this.

Chapter 3 Materials and Methods

3.1 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were determined prior to the commencement of the literature search. Studies were considered for inclusion if the met the following criteria:

- Randomised controlled trial (RCT) study design;
- Primary comparison made between early feeding and traditional (nil-by-mouth) postoperative nutritional management. Early feeding was defined as the provision of nutritionally significant oral or enteral nutrition via nasogastric or jejunal feeding tube, provided within 24-hours postoperatively. Examples of nutritionally significant oral nutrition included free fluids or standard hospital diet; clear fluids were not included due to its lack of protein and inability to meet nutritional requirements irrespective of volume consumed (Hancock *et al*., 2002). Traditional postoperative management was defined as withholding nutritional provision until bowel function had resumed, as evidenced by either passage of flatus or bowel motion. The presence of a nasogastric tube to provide gastric decompression, which is commonly used in association with traditional postoperative management, was not considered necessary for inclusion;
- Early feeding provided proximal to the anastomosis;
- Surgery performed on patients undergoing elective gastrointestinal resections – no restrictions were placed on the reason for surgery (i.e. malignant versus non-malignant surgical indications);
- Surgery performed in an adult population (defined as >18 years of age);
- Published in the English language; and
- Reporting on clinically relevant outcomes.

Studies were excluded from the analysis if they failed to meet any of the above criteria. Unpublished studies and abstracts presented at national and international meetings were excluded. Similarly, duplicate publications were also excluded. Additional exclusion criteria included use of immune-enhancing enteral feed products such as Oral Impact® (Nestle Healthcare Nutrition, Minneapolis, USA) as these may independently improve postoperative outcomes in some patient populations (Zheng *et al*., 2007). Similarly, research utilising parenteral nutrition in either study group were excluded as routine parenteral nutrition has been implicated in increased postoperative complications when compared with both postoperative enteral feeding (Torosian, 1999) and nil-by-mouth management (Veterans Affairs Total Parenteral Nutrition Cooperative Study Group, 1991). Parenteral nutrition also provides a source of nutrition that is not available to those receiving the traditional nil-by-mouth interventions so may influence results.

3.2 *Literature Search*

A thorough literature search was conducted utilising a wide range of electronic databases. Medline, Pubmed, Embase, CINAHL, Cochrane Register of Systematic Reviews, Science Citation Index, and Google Scholar were cross-searched using search the following search terms: 'early feeding', 'colorectal', 'gastric', 'gastrointestinal', 'upper GI', 'RCT', 'postoperative', 'early postoperative feeding', 'randomis/zed', 'prospective', 'oral feeding', 'surgery', 'nutrition'. Search terms were customised to suit each search engine in an attempt to detect relevant English language papers comparing the outcomes of early postoperative feeding in resectional surgery with traditional postoperative nutritional management. Appendix A outlines the combinations utilised for different databases. All available year limits were included. Additional limits specifying RCTs, meta-analyses and age groups 19-80+ were applied to combinations of the outlined search terms. Reference lists of review papers and existing meta-analyses were hand searched for further appropriate citations.

3.3 *Evaluation of Methodological Quality*

Evaluation of methodological quality of identified studies was conducted using the validated Jadad scoring scale (Jadad *et al*., 1996). This method assigns a score of between zero (lowest quality) and five (highest quality) to a study based on the reporting of randomisation, blinding, and withdrawals (Jadad *et al*., 1996). To obtain a maximum score studies must state they are randomised (1 point) with an appropriate method of randomisation (1 point), be described as double blinded (1 point) and report using a suitably robust method to achieve this (1 point), and report withdrawals or drop-outs from the study (1 point) (Jadad *et al*., 1996). Points can also be deducted if inappropriate methods of randomisation or double blinding are utilised (Jadad *et al*., 1996).

3.4 *Data Extraction and Reporting*

A standardised data extraction form was created to reflect the inclusion criteria and Jadad scoring system prior to the commencement of retrieving the papers identified in the literature searches (Jadad *et al*., 1996). (See Appendix B). Retrieved papers were appraised for compliance with inclusion criteria and methodological quality. Data were recorded in accordance with the recommendations from the Quality of Reporting of Meta-analyses (QUOROM) group (Moher *et al*., 1999). These recommendations promote a transparent reporting of the processes and outcomes of meta-analyses conducted on RCTs and involve a 21-point checklist of aspects pertaining to the meta-analysis and included studies (Moher *et al*., 1999). A cornerstone of the QUOROM recommendations is the development and inclusion of a QUOROM statement which tracks the process and rational for exclusion of studies from those identified through literature searches (Moher *et al*., 1999). Data obtained from each included trial were tabulated in an Excel (Microsoft® 2007) spreadsheet by outcome in preparation for statistical analysis (Appendix C).

3.5 *Outcomes Assessed*

Outcomes sought for assessment were those considered to exert influence over practical aspects of surgical practice and policy decisions within institutions such as rates of postoperative complications, mortality outcomes, patient tolerance of early feeding, resumption of bowel function, and length of hospital stay as identified in sections 2.2 and 2.3. All studies reporting on any outcomes of this nature were considered and final analyses were conducted on outcomes where numbers were sufficient to allow statistical analysis. Where required, authors were contacted for clarification of data or additional information.

3.6 Obtaining Additional Information from Authors

When additional information or clarification was required from authors of studies being considered for inclusion an initial e-mail or letter outlining the data required and the reason for the request was sent to the corresponding author address on the paper. On the occasions when e-mails were returned undelivered, a letter was sent to the mailing address of the institution of the corresponding author. If not response was received after a month, a follow-up letter was sent reiterating the request. In the event that no response was received after the second correspondence, an internet search for contact details of the corresponding or other authors was attempted and if successful, further attempts were made by e-mail to elicit the information required. A deadline of the end of December 2008 was set for information to be provided.

3.7 *Statistical Analysis*

All estimates were obtained using computer programs written in R (Hornik, 2008). All plots were obtained using the 'rmeta' package (Lumley, 2008). In the case of tests of hypotheses, *P*-values reported for different study variables were considered to be statistically significant at 0.05.

3.7.1 Statistical Model Applied to the Meta-analysis

The random effects model, developed by using the inverse variance weighted method approach (Sutton *et al*., 2000), was used to compute the combined effects from the included data. The random effects model can be described as

$$T_i = \mu_\theta + u_i + e_i \ , \qquad (3.1)$$

where T_i represents the effect estimate, μ_θ the true mean, u_i the between study variance and e_i the within-study variance (Huedo-Medina *et al*., 2006). The weighted inverse variance may be expressed as

$$w_j = \frac{1}{v_j + \tau^2} \ , \qquad (3.2)$$

where w_j is the weight attributed to study variable j , v_j is the within-study variance and τ^2 is the between-studies variance (Borenstein *et al*., 2007).

3.7.2 *Statistical Analysis of Outcome Variables*

Binary outcome variables were evaluated using odds ratios (OR). Conceptually the OR is defined as the odds of a specified event occurring in the control group divided by the odds of a specified event occurring in the intervention group (Higgins and Green, 2006a). This can be calculated as described from Table 3.1 and equations 3.3 a, b and c (Petrie and Sabin, 2000).

Table 3.1 Calculation of OR from a two-way table

	Event	No Event	Total
Intervention	*a*	*b*	*a + b*
Control	*c*	*d*	*c + d*

$$\mathbf{odds}_{\mathbf{control}} = \frac{\left(\frac{a}{a+c}\right)}{\left(\frac{c}{a+c}\right)} = \frac{a}{c} \quad (3.3a)$$

$$\mathbf{odds}_{\mathbf{intervention}} = \frac{\left(\frac{b}{b+d}\right)}{\left(\frac{d}{b+d}\right)} = \frac{b}{d} \quad (3.3b)$$

$$\mathbf{OR} = \frac{\frac{a}{c}}{\frac{b}{d}} = \frac{ad}{bc}, \quad (3.3c)$$

An amended estimator of the OR, namely the addition of 0.5 to each cell, was used to avoid the computation of reciprocal of zeros among observed values (Agresti, 1996).

Effect measures of continuous variables were evaluated using the weighted mean difference (WMD). Weighted means were obtained using the following formula

$$\overline{T.} = \frac{\sum_{i=1}^{k} w_i T_i}{\sum_{i=1}^{k} w_i}, \quad (3.4)$$

in which $\overline{T.}$ is the weighted mean, w_i is the weight assigned to each study utilising the random effects model of meta-analysis (see equation 3.1), and T_i is the observed effect of each study (Borenstein *et al*., 2007). WMD was calculated via

$$\mathbf{WMD} = \frac{w_i\left(\overline{T.}_{int} - \overline{T.}_{con}\right)}{\sum w_i}, \quad (3.5)$$

where $\overline{T.}_{int}$ is the weighted mean of the intervention group, $\overline{T.}_{con}$ is the weighted mean of the control group and w_i is the weight attributed to the study variable (Sutton *et al*., 2000).

The 95% confidence interval for the combined effect was computed

$$\textbf{Upper limit} = \bar{T}_. - 1.96 * SE(\bar{T}_.) \tag{3.6a}$$

$$\textbf{Lower limit} = \bar{T}_. + 1.96 * SE(\bar{T}_.) , \tag{3.6b}$$

where $\bar{T}_.$ is the weighted mean and $SE(\bar{T}_.)$ is the standard error of the weighted mean (Borenstein *et al*., 2007). Standard error for this equation was calculated using the following method

$$SE(\bar{T}_.) = \sqrt{\frac{1}{\sum_{i=1}^{k} w_i}} , \tag{3.7}$$

where $SE(\bar{T}_.)$ is the standard error of the weighted mean and w_i is the weight assigned to each study using the random effects model as described in equation 3.1 (Borenstein *et al*., 2007). Alternatively, this can be described as the square root of the variance of the combined effect (Borenstein *et al*., 2007). For the calculations of the confidence intervals estimates of mean and standard deviation are required. However, some of the published trials did not report the mean and standard deviation, but rather reported the size of the trial, median and range. From these available statistics, estimates of the mean and standard deviation were obtained using formulas proposed by Hozo *et al* (2005).

The Z-value of each outcome measure was computed to obtain a measure of statistical significance. This can be expressed as

$$Z = \frac{\bar{T}_.}{SE(\bar{T}_.)} , \tag{3.8}$$

where Z is the standardised value, $\bar{T}_.$ is the weighted mean and $SE(\bar{T}_.)$ is the standard error of the weighted mean (Borenstein *et al*., 2007). *P*-values for this test were calculated using a two-tailed test and the equation described below

$$p = 2[1 - \phi(|Z|)] , \tag{3.9}$$

in which ϕ is the *"standard normal cumulative distribution function"*, and Z is the standardised value for the weighted mean (Borenstein *et al*., 2007, p.17).

3.7.3 Tests of Heterogeneity

Heterogeneity among studies was assessed using the Q statistic (Cochran, 1954; Hedges and Olkin, 1985; Sutton *et al*., 2000) and I^2 index (Higgins and Thompson, 2002; Huedo-Medina *et al*., 2006).

The Q statistic is defined as

$$Q = \sum_{i=1}^{k} w_i (T_i - \bar{T})^2 , \qquad (3.10)$$

where w_i is the individual weighting assigned to each included study (described as the inverse variance of the between-study variation and within-study variation), T_i is the observed effect, $\bar{T}$ is the observed mean and k is the number of studies included in the meta-analysis (Huedo-Medina *et al*., 2006). Results are considered to be statistically significant when the observed value of Q is equal or larger than the critical value of χ^2 with (k-1) degrees of freedom at a given significance level (〈), in this case 0.05. The null hypothesis of a Q test is homogeneity (Cochran, 1954; Huedo-Medina *et al*., 2006).

The I^2 Index describes the proportion of variation across studies due to between-study heterogeneity rather than chance. The expression of the I^2 Index may be described

$$I^2 = \frac{Q - (k-1)}{Q} \times 100 \%, \qquad (3.11)$$

where Q is the Q statistic described in equation 3.10, and k is the number of studies included in the meta-analysis (Huedo-Medina *et al*., 2006).

Heterogeneity was further explored based on year of publication. Subgroup analysis was performed by stratifying studies into groups on the basis of publication before or after the year 2000.

3.7.4 Assessment of Publication Bias

Funnel plots were constructed for each outcome variable using the ‘rmeta’ package in order to assess the presence of publication bias in the meta-analysis. Total sample size, standard error and precision were plotted against the treatment effects of variables using the log OR or WMD as appropriate for the variable (Egger *et al*., 1997b; Sutton *et al*., 2000; Tang and Liu, 2000). For the funnel plots plotted against the standard error, 95% confidence interval lines were also included to allow for a more objective visual assessment of compliance with the funnel shape.

Chapter 4 Results

4.1 Literature Search and Study Selection

Cross searching of the electronic databases yielded 87 unique abstracts of potential relevance which were retrieved for review. Figure 4.1 presents the results of the study selection following the Quality of Reporting of Meta-analyses (QUOROM) recommendations (Moher *et al*., 1999).

4.1.1 Excluded Studies

Forty-one studies failed to meet the criteria of being randomised controlled trials (RCT) and were excluded from the analysis. These included three editorials (Fanning and Andrews, 2001; Ortiz *et al*., 1995; Silk and Gow, 2001), three correspondences (Gatt and MacFie, 2007; Parker, 1997; Wexner, 1996), two retrospective studies (Aiko *et al*., 2005; Choi and O'Connell, 1996), 19 prospective observational studies (Aihara *et al*., 2003; Basse *et al*., 2002; Buchmann *et al*., 1998; Bufo *et al*., 1994; Detry *et al*., 1999; DiFronzo *et al*., 2003; Hedberg *et al*., 1999; Kasparek *et al*., 2004; Kawamura *et al*., 2000; King *et al*., 2006; MacKay *et al*., 2007; Petrelli *et al*., 2001; Raue *et al*., 2004; Seenu and Goel, 1995; Stephen and Berger, 2003; Suehiro *et al*., 2004) of which three were in abstract form (Arthur *et al*., 2004; Dalmia *et al*., 2001; Kehlet *et al*., 2004), eight review articles (Alves *et al*., 2004; Ashrafi and Pochin, 2007; Bisgaard and Kehlet, 2002; Lassen and Revhaug, 2006; Ng and Neill, 2006; Nygren *et al*., 2003; Sands and Wexner, 1999; Wu and Griffiths, 2005) and one experimental study conducted in animal subjects (Kiyama *et al*., 2000). Five meta-analyses were also identified and excluded (Andersen *et al*., 2006; Charoenkwan *et al*., 2007; Lewis *et al*., 2008; Lewis *et al*., 2001; Wind *et al*., 2006a).

The reference lists in the three meta-analyses investigating early versus traditional feeding in colorectal resectional surgery were reviewed for additional citations (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001): one RCT not identified through the database search was located through this means (Schroeder *et al*., 1991).

Of the 46 RCTs identified a further 31 more were excluded for not meeting the inclusion criteria. Eight reported on non-gastrointestinal surgery (gynaecological (Cutillo *et al*., 1999; Pearl *et al*., 2002; Pearl *et al*., 1998; Schilder *et al*., 1997; Steed *et al*., 2002) including two in abstract form (Pearl, 1997; Pearl *et al*., 1999) and laryngectomies (Seven *et al*., 2003)) and two reported on gastrointestinal surgery under emergency conditions (Malhotra *et al*., 2004; Singh *et al*., 1998). Two RCTs identified made primary comparisons between the outcomes of open and laparoscopic surgical techniques (Ortiz *et al*., 1996a; Schwenk *et al*., 1998) while one investigated jejunal versus gastric feeding in non-surgical critically ill patients (Montejo *et al*., 2002). Of the RCTs in elective gastrointestinal resectional surgery, four were excluded for not meeting the definition of early feeding (Beattie *et al*., 2000; Bickel *et al*., 1992; Smedley *et al*., 2004; Tsunoda *et al*., 2005), two for providing nutrition not considered to be nutritionally adequate within the first postoperative day (Feo *et al*., 2004; Reissman *et al*., 1995) and five for providing nutritionally adequate nutrition distal to the surgical anastomosis (Aiko *et al*., 2001; Heslin *et al*., 1997; Lobo *et al*., 2006; Senkal *et al*., 1997; Watters *et al*., 1997). In the

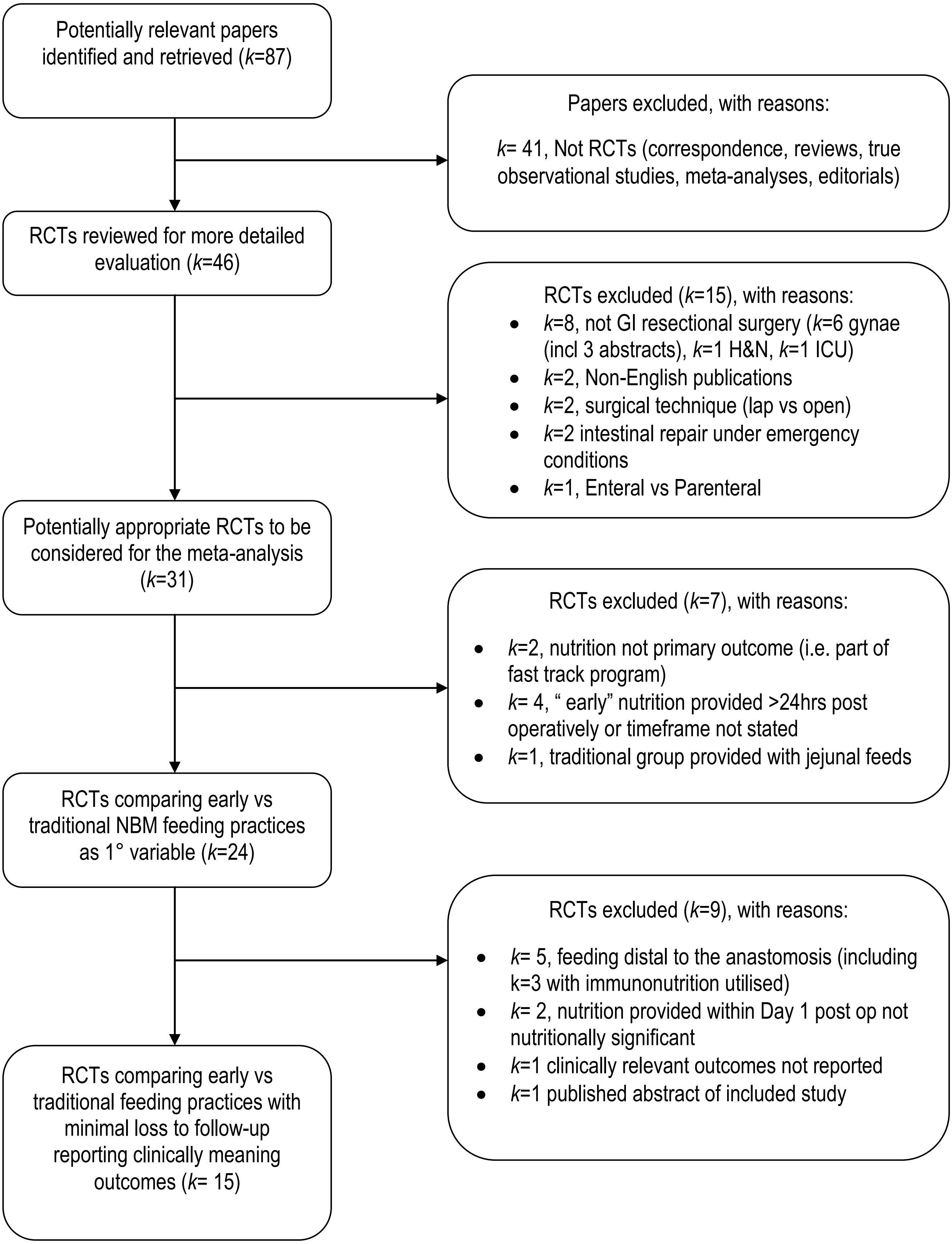

Figure 4.1 Quality of Reporting of Meta-analyses (QUOROM) Statement showing the flow of eligible studies for inclusion into the meta-analysis.RCT=Randomised Controlled Trial; NBM=Nil-By-Mouth

latter case, three studies also utilised immune-enhancing formulas (Heslin *et al*., 1997; Lobo *et al*., 2006; Senkal *et al*., 1997). Further RCTs conducted in gastrointestinal surgery were excluded from the analysis for comparing outcomes of enteral nutrition with parenteral nutrition (Gabor *et al*., 2005) or for comparing oral intake with jejunal feeding within the early feeding period (Lassen *et al*., 2008). Two studies that did not report on nutritional parameters as their primary outcomes were excluded (Henriksen *et al*., 2002a; Henriksen *et al*., 1998). Two studies were excluded for not reporting clinically relevant outcomes (Hochwald *et al*., 1997; Watters *et al*., 1997) and one was excluded for being an abstract form of a study reported in full (Binderow *et al*., 1993).

Despite English language limits being set, five studies not published in their entirety in English were identified (Alves *et al*., 2004; Buchmann *et al*., 1998; de Aguilar-Nascimento and Goelzer, 2002; Detry *et al*., 1999; Hiratsuka *et al*., 2003). Of these, two were potentially relevant RCTs, however, attempts to acquire their full articles or translations were unsuccessful (de Aguilar-Nascimento and Goelzer, 2002; Hiratsuka *et al*., 2003).

4.1.2 Included Studies

Fifteen studies covering a time period of 28 years from 1979 to 2007 fulfilled the inclusion criteria and were included in the meta-analysis (Beier-Holgersen and Boesby, 1996; Binderow *et al*., 1994; Carr *et al*., 1996; Delaney *et al*., 2003; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Lucha *et al*., 2005; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Ryan *et al*., 1981; Sagar *et al*., 1979; Schroeder *et al*., 1991; Stewart *et al*., 1998; Zhou *et al*., 2006). The details of each included study are summarised in Table 4.1. Pooled results yielded 1240 patients, with a near even distribution between feeding interventions (n=617 traditional postoperative management, n=623 early post operative feeding. A median sample size of 60 participants (range, 14-316) was noted for included studies.

4.1.2.1 Correspondence With Authors of Included Studies

Dr Ingrid Han-Geurts, the corresponding author from the two Han-Geurts *et al* (2001; 2007) studies was contacted for permission to access information for their gastrointestinal surgery patients (in view of the fact 25% of their sample were vascular patients). This was kindly provided for the 2007 study. Access to these data also allowed the mean and standard deviation of outcomes for the gastrointestinal surgical patients to be determined, thus avoiding the need to estimate these using the reported sample size, median and range values. Data from their 2001 study were also requested, but were unable to be provided.

Correspondence with Dr Carlo Feo regarding the nature of the liquid diet utilised for his study (Feo *et al*., 2004) indicated that only water, tea and vegetable soup was provided in the first 24-hours postoperatively (Feo, 2008). This study would otherwise have met the inclusion criteria, but was subsequently excluded for not providing nutritionally adequate fluids within the early postoperative feeding period.

Postoperative vomiting outcomes were reported without actual numbers of patients affected in Figure 2 of Ortiz *et al* (1996b, p. 121), however, correspondence with Dr Ortiz resulted in the percentage of patients being made available (Ortiz, 2008). These percentages were converted into patient numbers through multiplying the percentage with the documented number of patients in each intervention arm.

Dr Richard Frazee, Dr Conor Delaney, Mr RJ Woods and Dr Tong Zhou were also contacted for additional information about the Hartsell *et al* (1997), Delaney *et al* (2003), Stewart *et al* (1998) and Zhou *et al* (2006) studies respectively. All attempted correspondence was either returned due to the addressee no longer at that address (as in the case with Drs Frazee and Delaney) or unanswered (as with Mr Woods and Dr Zhou). Attempts to obtain current correspondence details of the corresponding authors were unsuccessful. In the absence of this information, it was assumed that liquid diets provided within 24-hours postoperatively were nutritionally adequate in the Delaney *et al* (2003), Hartsell *et al* (1997) and Zhou *et al* (2006) studies. Similarly, the lack of response from the authors of the Stewart *et al* (1998) study resulted in the discrepancy noted in the reported numbers of complications between the text and Table 6 to be analysed using the Figures in Table 6 (p. 127).

4.1.2.2 Methodological Quality of Included Studies

None of the 15 included studies achieved a Jadad score of over three (median, 2; range, 1-3). Six studies described the method of randomisation (Carr *et al*., 1996; Han-Geurts *et al*., 2001, 2007; Nessim *et al*., 1999; Stewart *et al*., 1998), six reported on withdrawals (Carr *et al*., 1996; Han-Geurts *et al*., 2007; Ortiz *et al*., 1996b; Ryan *et al*., 1981; Schroeder *et al*., 1991; Stewart *et al*., 1998), and one study reported on blinding (Beier-Holgersen and Boesby, 1996).

4.2 Outcome Variables for Statistical Analysis

Outcomes with insufficient data to allow analysis included cost savings, weight loss, caloric and protein intake, nitrogen balance, quality of life, duration to resumption of bowel sounds, postoperative abdominal distension, days to commencement of diet, diet tolerance at first attempt, duration to tolerance of solid diet, wound healing, muscle function, postoperative fatigue, time to reinsertion of nasogastric tube and rates of hospital readmission. Sufficient data were available for the analysis for eight clinically relevant outcomes. These are outlined in the subsections below.

4.2.1 Mortality

All 15 studies involving 1240 patients reported on mortality. A 29% reduction in relative odds of in-hospital postoperative mortality was observed with early feeding when compared with traditional postoperative feeding practices. However, this trend did not achieve statistical significance (OR 0.71; 95% Confidence Interval (CI) 0.32, 1.56; p=0.39). Stratifying for year of publication demonstrated differences between pre- and post-2000 publications, although these also failed to reach statistical significance; pre-2000 studies more strongly favoured early feeding than did post-2000 studies (OR 0.58; CI 0.22, 1.54; p=0.27 and OR 1.03; CI

0.27, 3.88; *p*=0.96 respectively). No heterogeneity was observed in pooled or stratified results (Q =4.24, *p*=0.99; Q =0.85, *p*=0.99; Q =2.93, *p*=0.56 for pooled, pre-2000 and post-2000, respectively; I^2 for all 0%; CI 0%-71.6% for post-2000 and no variation detected for pre-2000 and pooled data). See forest plot, Figure 4.2.

Study	Early	Traditional	OR	L	U
pre 2000					
Sagar	0 of 15	0 of 15	1	0.02	53.66
Ryan	0 of 7	0 of 7	1	0.02	57.31
Schroeder	0 of 16	0 of 16	1	0.02	53.46
Binderow	0 of 32	0 of 32	1	0.02	51.94
Beier-Holgersen	2 of 30	4 of 30	0.52	0.1	2.65
Carr	0 of 14	1 of 14	0.31	0.01	8.29
Ortiz	0 of 93	0 of 95	1.02	0.02	52.01
Hartsell	0 of 29	1 of 29	0.32	0.01	8.24
Nessim	0 of 27	0 of 27	1	0.02	52.22
Stewart	0 of 40	1 of 40	0.33	0.01	8.22
subtotal	**2 of 303**	**7 of 305**	**0.58**	**0.22**	**1.54**
post 2000					
Han-Geurts	0 of 56	3 of 49	0.12	0.01	2.33
Delaney	0 of 31	0 of 33	1.06	0.02	55.24
Lucha	0 of 26	0 of 25	0.96	0.02	50.35
Zhou	0 of 161	0 of 155	0.96	0.02	48.83
Han-Geurts	3 of 46	1 of 50	2.66	0.38	18.77
subtotal	**3 of 320**	**4 of 312**	**1.03**	**0.27**	**3.88**
POOLED	**5 of 623**	**11 of 617**	**0.71**	**0.32**	**1.56**

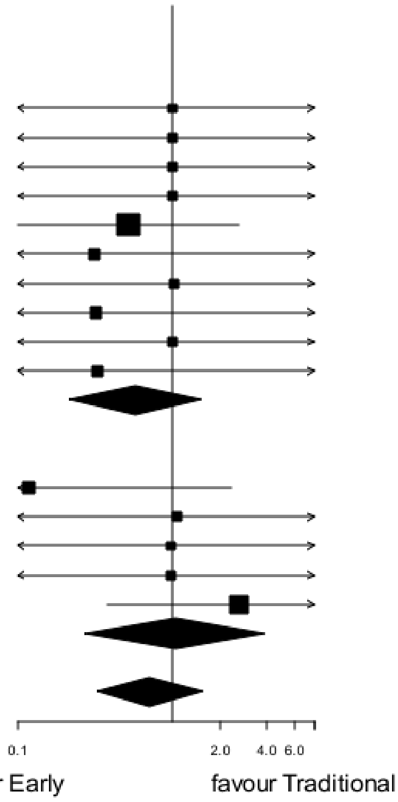

Figure 4.2 – Forest Plot of Mortality. Values in the left panel represent the observed counts for early vs traditional feeding practices, odds ratio and limits of 95% confidence intervals for odds ratio of the outcome variable. In the graph the squares indicate point estimates of the treatment effect with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence intervals for odds ratios of individual studies. The pooled estimate for mortality is the pooled odds ratio obtained by combining all odds ratios of the 15 studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at 1.0 favour early feeding.

4.2.2 Postoperative Complications

All 15 studies included reported on postoperative complications, involving data from 1240 patients. As illustrated by the forest plot (Figure 4.3), pooled results demonstrate significantly fewer patients developed postoperative complications if they received early feeding when compared with traditional postoperative management (OR 0.55; CI 0.35, 0.87; *p*=0.01). When stratified for year of study publication similar trends were observed in both the pre- and post-2000 datasets (OR 0.55; CI 0.34, 0.90; *p*=0.01 and OR 0.62; CI 0.26, 1.51; *p*=0.29 respectively), however statistical significance was not reached in the post-2000 data.

Significant heterogeneity was noted in pooled results and in the post-2000 group (Q =29.07; *p*=0.01; I^2 =51.8%; CI 13.15%-73.25% and Q =17.78; *p*=0.001; I^2=77.5%, CI 45%-90.68% respectively). This was not observed in the pre-2000 data (Q =10.61; *p*=0.3; I^2 =15%; CI 0%-

45.47%). In each case, the I^2 index indicates moderate to high heterogeneity attributed to between-study variations.

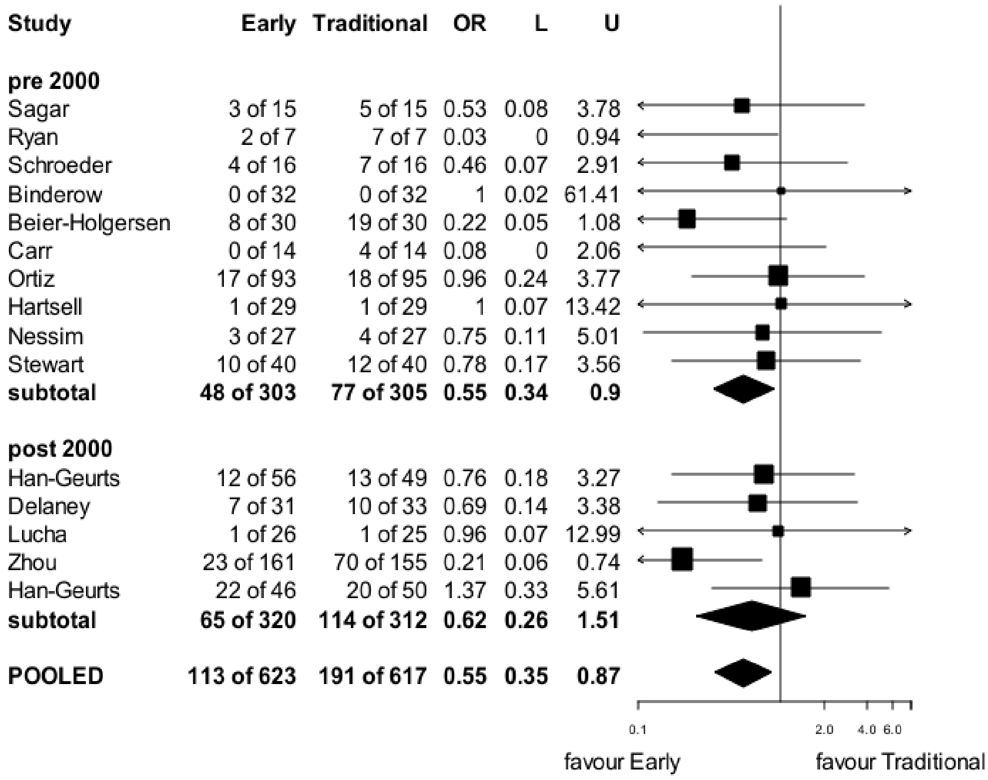

Figure 4.3 – Forest Plot of Postoperative Complications. Values in the left panel represent the observed counts for early vs traditional feeding practices, odds ratio and limits of 95% confidence intervals for odds ratio of the outcome variable. In the graph the squares indicate point estimates of the treatment effect with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence intervals for odds ratios of individual studies. The pooled estimate for the complication rate is the pooled odds ratio obtained by combining all odds ratios of the 15 studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at 1.0 favour early feeding.

4.2.3 Anastomotic Dehiscence

Thirteen studies involving a total of 1075 patients reported on rates of anastomotic dehiscence (Beier-Holgersen and Boesby, 1996; Carr *et al*., 1996; Delaney *et al*., 2003; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Lucha *et al*., 2005; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Sagar *et al*., 1979; Schroeder *et al*., 1991; Stewart *et al*., 1998; Zhou *et al*., 2006). A 25% reduction in relative odds favouring early feeding was observed in pooled results, however, this did not reach statistical significance (OR 0.75; CI 0.39, 1.45; p=0.39). Stratification for year of publication resulted in the pre-2000 data showing stronger trends favouring early feeding (OR 0.62; CI 0.25, 1.52; p=0.29) compared with post-2000 data (OR 0.93; CI 0.36, 2.43; p=0.88). No heterogeneity was observed in pooled or stratified results (Q =3.31, p=99; Q =1.50, p=0.98; Q =1.44, p=0.83 for pooled, pre-2000 and post-2000 respectively; I^2 for all 0%, and no variation detected for pre-2000 and pooled data, 0%-42.23% in post-2000 subgroup). See forest plot, Figure 4.4.

Table 4.1 – Summary of Studies Included in the Meta-analysis

Included Study (Author)	Year	Patient population	n (trad/early)	Jadad Score	Early feeding protocol
Sagar *et al*	1979	Major intestinal surgery – oesophagogastrectomy (*n*=2), gastrectomy (*n*=6), colectomy, anterior resection, abdominoperineal resection	15/15	1	½ strength Flexical® (elemental feed product) @ 25ml/hr for 24hrs D1 post op, full strength Flexical® @ 25ml/hr for 24hrs D2 post op, full strength Flexical® @ 50ml/hr for 24hrs D3 post op, full strength Flexica®l @ 100mL/hr D4 post op via jejunal port of nasogastric/jejunal tube
Ryan *et al*	1981	Partial colectomy	7/7	2	Vivonex HN® (elemental feed product) 10% w/v @ 50mL/hr on day of operation, 10% w/v @100mL/hr D1 post op, 10% w/v @125mL/hr D2, 15% w/v @ 125mL/hr D3, 20% w/v @ 125mL/hr D4, 20% w/v @ 125mL/hr D5, 25% w/v @ 125mL/hr D6 & D7
Schroeder *et al*	1991	Small or large bowel resections or reanastomosis – colonic resection, abdominoperineal resection, ileoanal J pouch, small bowel resection	16/16	2	50mL/hr Osmolite® day of operation, 80mL/hr Osmolite® if tolerated thereafter. Oral intake D3 post op
Binderow *et al*	1993	Laparoscopic assisted Laparotomy with colonic or ileal resection	32/32	1	Regular diet from D1 post op
Beier-Holgersen *et al*	1996	Gastrointestinal disease treated with bowel resection with anastomosis, enterostomy, gastric (*n*=5) or oesophageal resection (*n*=3).	30/30	2	Clear fluids orally + increasing volumes of Nutridrink® via nasojejunal tube from day of surgery
Carr *et al*	1996	Unspecified intestinal surgery	14/14	3	Immediate post op nasojenunal feeding – 25ml/hr Fresubin® (1kcal/mL) and increased by 25ml/hr q4h until individual caloric goals met
Ortiz *et al*	1996	Laparotomy for colon or rectal surgery	95/93	2	Clear fluids on day of surgery (?pre/post op), Regular diet from D1 post op
Hartsell *et al*	1997	Open colorectal surgery	29/29	1	Full liquid diet D1 post op, regular diet once tolerating >1L in 24hrs

Included Study (Author)	Year	Patient population	n (trad/early)	Jadad Score	Early feeding protocol
Nessim *et al*	1997	Anorectal reconstructive surgery	27/27	2	Regular diet from D1 post op
Stewart *et al*	1998	Colorectal resection with anastomosis and without stoma formation	40/40	3	Free fluids from 4 hours post op on day of surgery, Regular diet from D1 post op
Han-Geurts *et al*	2001	Abdominal surgery (vascular + colonic)	49/56	2	Regular diet from D1 post op
Delaney *et al*	2003	segmental intestinal or rectal resection by laparotomy, including reoperation or pelvic surgery and those with comorbidities	33/31	2	Fluid diet D1 post op with regular diet in PM of D1 post op
Lucha *et al*	2005	Open colorectal surgery	25/26	1	Regular diet from 8hrs day of surgery
Zhou *et al*	2006	Excision and anastomosis for colorectal tumour	155/161	1	Liquid fibreless diet D1-3 post op
Han-Geurts *et al*	2007	Open colorectal surgery	50/46	3	Regular diet from D1 post op

w/v= weight for volume; D1=Day 1; D2=day 2; D3=Day 3; D4=Day 4; D5=Day 5; D6=Day 6; D7=Day 7; q4h=4th hourly; kcal=kilocalorie

Study	Early	Traditional	OR	L	U
pre 2000					
Sagar	0 of 15	1 of 15	0.31	0.01	8.29
Schroeder	0 of 16	0 of 16	1	0.02	53.46
Beier-Holgersen	2 of 30	4 of 30	0.52	0.1	2.65
Carr	0 of 14	0 of 14	1	0.02	53.89
Ortiz	2 of 93	4 of 95	0.56	0.12	2.68
Hartsell	0 of 29	1 of 29	0.32	0.01	8.24
Nessim	0 of 27	0 of 27	1	0.02	52.22
Stewart	1 of 40	0 of 40	3.08	0.12	77.8
subtotal	**5 of 264**	**10 of 266**	**0.62**	**0.25**	**1.52**
post 2000					
Han-Geurts	2 of 18	1 of 19	1.87	0.22	15.73
Delaney	0 of 31	0 of 33	1.06	0.02	55.24
Lucha	1 of 26	0 of 25	3	0.12	77.17
Zhou	2 of 161	4 of 155	0.53	0.11	2.52
Han-Geurts	2 of 42	2 of 35	0.83	0.14	5.06
subtotal	**7 of 278**	**7 of 267**	**0.93**	**0.36**	**2.43**
POOLED	**12 of 542**	**17 of 533**	**0.75**	**0.39**	**1.45**

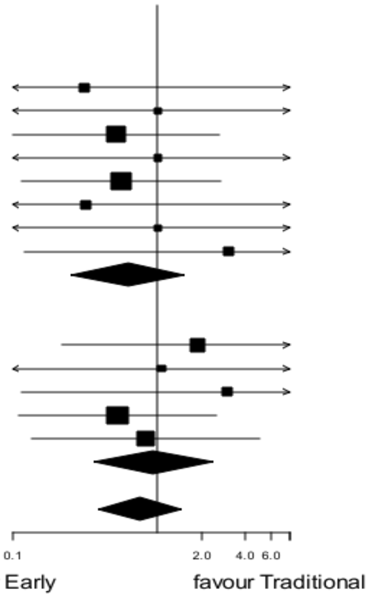

Figure 4.4 – Forest Plot of Anastomotic Dehiscence. Values in the left panel represent the observed counts for early vs traditional feeding practices, odds ratio and limits of 95% confidence intervals for odds ratio of the outcome variable. In the graph the squares indicate point estimates of the treatment effect with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence intervals for odds ratios of individual studies. The pooled estimate for the anastomotic dehiscence rate is the pooled odds ratio obtained by combining all odds ratios of the 13 studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at 1.0 favour early feeding.

4.2.4 Length of Hospital Stay

Ten studies with a total of 872 patients reported on the length of stay (LOS) in sufficient detail to allow inclusion in the analysis (Binderow *et al*., 1994; Carr *et al*., 1996; Delaney *et al*., 2003; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Sagar *et al*., 1979; Schroeder *et al*., 1991; Stewart *et al*., 1998; Zhou *et al*., 2006). Beier-Holgersen *et al* (1996), Nessim *et al* (1999) and Lucha *et al* (2005) reported mean or median values without providing standard deviations or ranges, so were unable to be included. Estimates of mean and standard deviation were made for Sagar *et al* (1979), Stewart *et al* (1998) and Han-Guerts *et al* (2001) using the median and range information reported. Mean and standard deviations were calculated using the raw data provided by the authors of the Han-Geurts *et al* (2007) study in preference to using the estimates obtained from using the reported median and ranges.

Trends toward a slightly shorter LOS were observed in patients receiving early feeding. A weighted mean difference (WMD) of -1.28 days (CI -2.94, 0.38; p= 0.13) was observed when data from all ten studies was analysed. When studies were stratified for year of publication, pre- and post-2000 data showed similar trends (WMD -1.05 days; CI -2.66, 0.56; p=0.2 and WMD -0.93; CI -3.95, 2.09; p=0.54). Significant heterogeneity was observed in the pooled (Q =61.19, p<0.0001; I^2 =85%, CI 74.73%-91.34%) and post-2000 result (Q =47.0, p<0.0001; I^2=93.6%, CI 56.85%-96.9%), while heterogeneity in pre-2000 studies approached significance (Q =10.17, p=0.07; I^2 =50.8%, CI 0%-80.44%). The high percentages of the I^2 index indicate the presence of a large degree of heterogeneity between studies. See forest plot presented in Figure 4.5.

Study	N	Early	N	Traditional	WMD	L	U
pre 2000							
Sagar	15	16.1(5.27)	15	23.8(11.86)	-7.67	-15.57	0.23
Schroeder	16	10.0(4.00)	16	15.0(10.0)	-5	-11.86	1.86
Binderow	32	6.70(3.25)	32	8.00(3.75)	-1.3	-6.01	3.41
Carr	14	9.80(6.60)	14	9.30(2.80)	0.5	-5.27	6.27
Hartsell	29	7.20(3.30)	29	8.10(2.30)	-0.9	-5.52	3.72
Stewart	40	12.8(7.25)	40	11.5(3.61)	1.33	-3.72	6.38
subtotal	**146**		**146**		**-1.05**	**-2.66**	**0.56**
post 2000							
Han-Geurts	56	24.5(21.92)	49	15.6(8.76)	8.9	1.27	16.53
Delaney	31	5.20(2.50)	33	5.80(3.00)	-0.6	-5.19	3.99
Zhou	161	8.40(3.40)	155	9.60(5.00)	-1.2	-5.68	3.28
Han-Geurts	46	12.0(1.80)	49	17.5(4.20)	-5.5	-10.07	-0.93
subtotal	**294**		**286**		**-0.93**	**-3.95**	**2.09**
POOLED	**440**		**432**		**-1.28**	**-2.94**	**0.38**

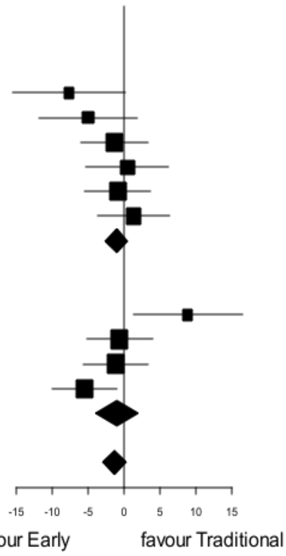

Figure 4.5 – Forest Plot for Length of Hospital Stay. Values in the left panel represent the sample size (n), mean (standard deviation), weighted mean difference and limits of the 95% confidence interval for the mean of the outcome variable. In the graph the squares indicate point estimates of the treatment effect with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence intervals for mean of individual studies. The pooled estimate for the length of days is the weighted mean difference obtained by combining mean differences of the 10 studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at 1.0 favour early feeding.

4.2.5 Development of Nausea and Vomiting

The presence of postoperative nausea and vomiting was reported in seven studies involving data from 532 patients, and these were all studies published prior to the year 2000 (Beier-Holgersen and Boesby, 1996; Binderow *et al*., 1994; Carr *et al*., 1996; Hartsell *et al*., 1997; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Stewart *et al*., 1998). To manage the variation in the reporting of these outcomes between studies, in cases where both nausea and vomiting were reported only outcomes for vomiting were included for analysis as it was thought that this would most accurately reflect the data desired. That is, patients may experience nausea without vomiting but rarely does vomiting occur without nausea. Analysis of these studies failed to demonstrate an effect of postoperative nutritional management on the presence of nausea and vomiting (OR 0.93; CI 0.53, 1.65; p=0.8). Heterogeneity is suggested by both the Q statistic and I^2 index, with a moderate presence of between-study variation indicated by the I^2 confidence intervals (Q =10.99; p=0.08; I^2= 45%; CI 0%-77.01%). However, these did not reach statistical significance. See forest plot, Figure 4.6.

Study	Early	Traditional	OR	L	U
pre 2000					
Binderow	14 of 32	8 of 32	2.26	0.8	6.39
Beier-Holgersen	19 of 30	22 of 30	0.64	0.22	1.88
Carr	1 of 14	7 of 14	0.11	0.02	0.79
Ortiz	13 of 93	8 of 95	1.73	0.69	4.29
Hartsell	16 of 29	15 of 29	1.14	0.41	3.15
Nessim	3 of 27	7 of 27	0.39	0.1	1.58
Stewart	14 of 40	14 of 40	1.00	0.4	2.47
POOLED	**80 of 265**	**186 of 267**	**0.93**	**0.53**	**1.65**

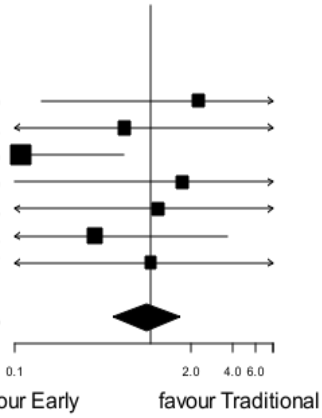

Figure 4.6 – Forest Plot of Incidence of Nausea and Vomiting. Values in the left panel represent the observed counts for early vs traditional feeding practices, odds ratio and limits of 95% confidence intervals for odds ratio of the outcome variable. In the graph the squares indicate point estimates of the treatment effect with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence intervals for odds ratios of individual studies. The pooled estimate for nausea and vomiting is the pooled odds ratio obtained by combining all odds ratios of the eight studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at 1.0 favour early feeding.

4.2.6 Nasogastric Tube Reinsertion

Eight studies involving 945 patients reported on the rates of nasogastric tube reinsertion, which can be considered a surrogate measure for the presence of postoperative nausea and/or vomiting (Binderow *et al*., 1994; Delaney *et al*., 2003; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Lucha *et al*., 2005; Stewart *et al*., 1998; Zhou *et al*., 2006). A 48% increase in relative odds of nasogastric tube reinsertion was noted with early feeding in pooled results, though this was not significant (OR 1.48; CI 0.93, 2.35; p=0.09). Similar results were seen when stratification was applied (Pre-2000 OR 1.61; CI 0.75, 3.44; p=0.22; Post-2000 OR 1.41; CI 0.78, 2.52; p=0.25). No heterogeneity was observed in any of the results (Pooled Q=3.24, p=0.86; Pre-2000 Q=0.05, p=0.97; Post-2000 Q=3.12, p=0.53; I^2 for all 0%, with no variation detected for pre-2000 subgroup, CI 0%-73.77% in post-2000 subgroup and CI 0%-29.95% for pooled results). See forest plot Figure 4.7.

In considering these results it is worth noting that despite nasogastric tubes normally being utilised for gastric decompression in traditional postoperative management, only the patients in the control group in the Zhou *et al* (2006) study retained their nasogastric tubes until there was evidence of resumption of bowel function. Of the remaining studies that report on rates of nasogastric reinsertion, nasogastric tubes were removed either in postoperative recovery or by the first postoperative day in the traditional management groups (Binderow *et al*., 1994; Delaney *et al*., 2003; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Lucha *et al*., 2005; Stewart *et al*., 1998).

Study	Early	Traditional	OR	L	U
pre 2000					
Binderow	6 of 32	4 of 32	1.55	0.42	5.78
Hartsell	8 of 27	5 of 27	1.78	0.52	6.11
Stewart	4 of 92	3 of 103	1.46	0.35	6.08
subtotal	**18 of 151**	**12 of 162**	**1.61**	**0.75**	**3.44**
post 2000					
Han-Geurts	9 of 56	9 of 49	0.85	0.32	2.3
Delaney	2 of 31	3 of 33	0.74	0.13	4.04
Lucha	5 of 26	3 of 25	1.64	0.38	7.11
Zhou	3 of 161	1 of 155	2.27	0.33	15.6
Han-Geurts	12 of 61	7 of 67	2.68	0.89	8.11
subtotal	**30 of 320**	**21 of 312**	**1.41**	**0.78**	**2.52**
POOLED	**48 of 471**	**33 of 474**	**1.48**	**0.93**	**2.35**

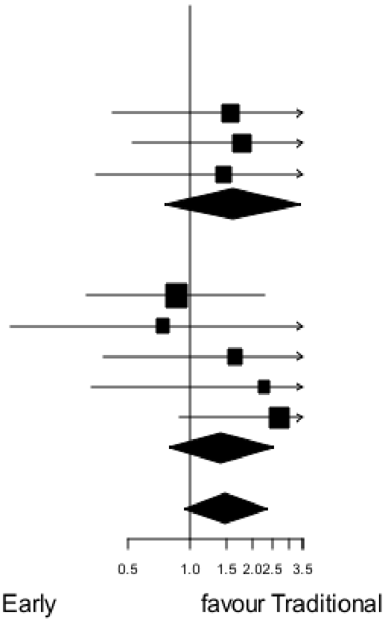

Figure 4.7 – Forest Plot for Nasogastric Tube Reinsertion. Values in the left panel represent the observed counts for early vs traditional feeding practices, odds ratio and limits of 95% confidence intervals for odds ratio of the outcome variable. In the graph the squares indicate point estimates of the treatment effect with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence intervals for odds ratios of individual studies. The pooled estimate for the nasogastric reinsertion rate is the pooled odds ration obtained by combining all odds ratios of the eight studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at 1.0 favour early feeding.

4.2.7 Days to Passage of Flatus

Four studies, including results from a total of 520 patients, reported on the number of days before passage of flatus occurred following surgery with sufficient information to allow for analysis (Han-Geurts *et al*., 2007; Schroeder *et al*., 1991; Stewart *et al*., 1998; Zhou *et al*., 2006). Binderow *et al* (1994), Beier-Holgerson *et al* (1996) and Carr *et al* (1996) reported mean or median values without standard deviation or ranges to allow for inclusion.

A WMD of -0.42 days (95%CI -1.12, 0.28; p=0.23) was observed for studies reporting on this outcome. When stratified for year of publication, passage of flatus was observed to occur significantly faster in the patients in the early feeding intervention in the pre-2000 subgroup (WMD -0.87 days; CI -1.33, -0.42; p=0.0002). However, this finding did not occur in the post-2000 data (WMD -0.14 days; CI -1.02, 0.74; p=0.75). Significant heterogeneity was observed in both the pooled (Q =75.63, p<0.001; I^2 =96%; CI 29.56%-97.88%) and post-2000 studies (Q =52.41, p<0.0001; I^2 =98.1%; CI 95.18%-99.18%) but not in the pre-2000 subgroup (Q =0.87, p=0.35; I^2 =0%; no variation detected). See forest plot, Figure 4.8.

Study	N	Early	N	Traditional	WMD	L	U
pre 2000							
Schroeder	16	2.41(1.33)	16	2.91(1.29)	-0.5	-2.09	1.09
Stewart	40	3.00(1.20)	40	4.00(1.20)	-1	-2.41	0.41
subtotal	**56**		**56**		**-0.87**	**-1.33**	**-0.42**
post 2000							
Zhou	161	3.00(0.90)	155	3.60(1.20)	-0.6	-1.93	0.73
Han-Geurts	43	1.70(0.20)	49	1.40(0.10)	0.3	-1.01	1.61
subtotal	**204**		**204**		**-0.14**	**-1.02**	**0.74**
POOLED	**260**		**260**		**-0.42**	**-1.12**	**0.28**

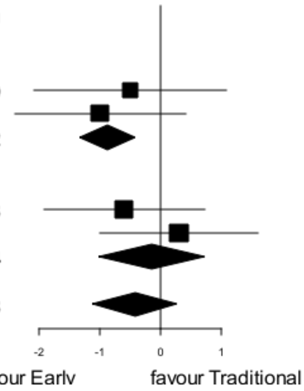

Figure 4.8 – Forest Plot for Passage of Flatus. Values in the left panel represent the sample size (n), mean (standard deviation), weighted mean difference and limits of the 95% confidence interval for the mean of the outcome variable. In the graph the squares indicate point estimates of the treatment effect with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence intervals for mean of individual studies. The pooled estimate for the length of days is the weighted mean difference obtained by combining all mean differences of the four studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at 1.0 favour early feeding.

4.2.8 Days to First Bowel Motion

The same four studies (and 520 patients) that reported combinable information on the number of days to passage of flatus also reported on the number of days until the first bowel motion occurred after surgery (Han-Geurts *et al*., 2007; Schroeder *et al*., 1991; Stewart *et al*., 1998; Zhou *et al*., 2006). Estimates of mean and standard deviation were made using the median and range data provided by Stewart *et al* (1998). A further seven studies reported on this outcome but in the absence of range or standard deviations (Beier-Holgersen and Boesby, 1996; Binderow *et al*., 1994; Carr *et al*., 1996; Han-Geurts *et al*., 2001; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Ryan *et al*., 1981).

A WMD of -0.28 days (95%CI -1.20, 0.64; p=0.55) was observed for all studies reporting on this outcome. When stratified for year of publication, a stronger trend toward earlier first bowel motion was observed in the patients in the early feeding intervention in the pre-2000 subgroup (WMD -0.55 days; CI -1.25, 0.15; p=0.12) than in the post-2000 subgroup (WMD -0.04 days; CI -1.32, 1.23; p=0.94). Neither of these achieved statistical significance. Significant heterogeneity was observed in both the pooled (Q =78.99; p<0.0001; I^2=96.2%; CI 92.94%-97.96%) and post-2000 studies (Q=70.15; p<0.001; I^2 =97.1%; CI 96.93%-99.34%) but not in the pre-2000 subgroup (Q=1.16; p=0.28; I^2 =0%; no variation detected). See forest plot, Figure 4.9.

Study	N	Early	N	Traditional	WMD	L	U
pre 2000							
Schroeder	16	3.21(1.50)	16	4.16(1.33)	-0.95	-2.93	1.03
Stewart	40	4.77(2.15)	40	5.00(1.80)	-0.23	-2.16	1.7
subtotal	**56**		**56**		**-0.55**	**-1.25**	**0.15**
post 2000							
Zhou	161	4.10(1.10)	155	4.80(1.40)	-0.7	-2.45	1.05
Han-Geurts	43	4.30(0.30)	49	3.70(0.30)	0.6	-1.13	2.33
subtotal	**204**		**204**		**-0.04**	**-1.32**	**1.23**
POOLED	**260**		**260**		**-0.28**	**-1.2**	**0.64**

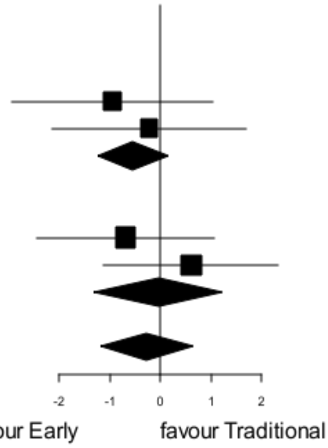

Figure 4.9 – Forest Plot for Days to First Bowel Motion. Values in the left panel represent the sample size (n), mean (standard deviation), weighted mean difference and limits of the 95% confidence interval for the mean of the outcome variable. In the graph the squares indicate point estimates of the treatment effect with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence intervals for mean of individual studies. The pooled estimate for the length of days is the weighted mean difference obtained by combining all mean differences of the four studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at 1.0 favour early feeding.

4.3 Publication Bias

Funnel plots displayed in Appendix D suggest the presence of publication bias in total complication rate, days passage of flatus, days to first bowel motion and LOS outcomes, as evidenced by points falling outside of the 95% confidence interval limits in plots of Log OR or WMD against standard error. Visual assessment of all the funnel plots constructed using Log OR or WMD versus precision or sample size appear asymmetrical which also suggests the presence of publication bias within the present work.

Chapter 5 Discussion

5.1 Outcomes of the Meta-analysis

5.1.1 Pooled Results

The point estimates obtained from this meta-analysis support the safety of providing enteral nutrition proximal to the anastomosis within 24-hours post elective gastrointestinal surgery and refute the concerns that provision of early feeding may increase the incidence of postoperative complications (Figures 4.2 to 4.9). The pooled findings suggest a statistically significant 45% reduction in relative odds of postoperative complications associated with the introduction of nutritionally significant food or fluid within 24-hours following surgery: this is the first meta-analysis to demonstrate this. Although not reaching statistical significance, early feeding was also associated with a relative reduction in the odds of mortality (29% relative odds reduction) and anastomotic dehiscence (25% relative odds reduction). Reduced weight mean differences (WMD) favouring early postoperative feeding were also observed for the outcomes of days to passage of flatus (-0.42 days), days to first bowel motion (-0.28 days) and length of stay (LOS) (-1.28 days) when compared with traditional management, however these did not reach statistical significance. The only adverse outcome observed with early feeding was a 48% increase in relative odds for incidence of nasogastric tube reinsertion, however, this was not statistically significant. In the context of the complications that appear to be reduced with early postoperative feeding, an increase in vomiting associated with this practice appears to be an issue of minor concern.

5.1.2 Results of Subgroup Analysis

Subgroup analyses with studies stratified for year of publication (pre-2000, post-2000) were conducted in an attempt to control for the impact of the evolution in perioperative practices occurring over the 28 years encompassed by studies included in the meta-analysis. The subgroup analyses demonstrated similar point estimates when compared with the pooled estimates, however, for total complications, mortality, anastomotic dehiscence, days to passage of flatus and bowel motion, and LOS outcomes results were seen to more strongly favour early feeding in the pre-2000 subgroup than in the post-2000 studies. Implications of statistical power may in part explain this observation.

However, there are other factors present within the studies comprising the subgroups that suggest numbers alone may not account for these differences. One possible explanation may be that the studies published prior to the year 2000 had not yet adopted many of the non-nutritional perioperative practices as standard practice. Should this be the case, the stronger trend favouring early feeding may be a purer indication of treatment effect associated with early feeding. However, it could also be argued that if increasing numbers of non-nutritional interventions promoting improved postoperative outcomes are being adopted over time, the effect of these confounders should move the point estimates more strongly in favour of the early feeding intervention in the post 2000 stratification. In this sense early feeding would be considered a surrogate measure of advances to peri- and postoperative care, however this does not appear to the case.

Another reason for the stronger results seen in the pre-2000 subgroup may be related to the number of patients receiving their early nutrition via a feeding tube versus oral intake. Of the 303 patients receiving an early nutrition intervention prior to the year 2000, 82 (27%) received tube feeding, while all patients in the post-2000 subgroup received early nutrition via voluntary oral intake (*n*=320). As tube feeding allows a greater control over the quantity of nutrition provided than voluntary oral intake, the early feeding patients in the pre-2000 subgroup may have received comparatively more nutrition than those in the post-2000 subgroup. The more favourable results seen in the pre-2000 subgroup, therefore, may be the result of a more adequate nutritional intake. Lack of reporting on nutritional intake in any of the studies in which oral intake was provided as the early nutritional intervention prevents stronger conclusions being drawn about this hypothesis.

Finally, the different trends in many of the outcome data reported in the two Han-Guerts *et al* (2001; 2007) studies – representing two of the five studies in the post-2000 subgroup – may contribute to the differences seen in the subgroup analysis. Possible explanations for the different outcomes in these two studies are described in section 5.3.1.1.

Only pre-2000 studies reported the incidence of nausea and vomiting in their patients. Large between-study variation was observed between early and traditional feeding intervention groups for these symptoms (7% to 63% and 30% to 73% respectively). Due to the different directions of the point estimates, the overall effect measure suggests no effect of early feeding on nausea and vomiting. The between-study variation observed is most likely explained by the different forms of nutrition support provided: two of the three point estimates that favoured early feeding for this outcome provided nutrition via a nasogastric tube. The slow, controlled provision of nutrition via a nasogastric tube may facilitate tolerance of early feeding when compared with larger food boluses consumed orally. Alternatively, gastric residual volumes may have been checked throughout the early feeding period in patients receiving nasogastric feeding, and large gastric volumes may have resulted in the cease of nasogastric feeds before nausea or vomiting could occur.

5.1.3 Choice of Summary Statistics

5.1.3.1 Binary Outcomes

Odds ratios (OR) were selected as the summary statistic to present binary outcomes as this is the traditional choice of effect measure in meta-analysis and it is considered to be the most robust summary statistic in terms of mathematical properties (Deeks, 2002). OR also yields less heterogeneity when compared with other summary statistics such as relative risk ratio (RR) and risk difference, and thus has been promoted by some authors on these grounds (Deeks, 2002). However, many meta-analyses conducted in clinical fields favour use of the RR over OR as RR is considered to be more instinctive in its interpretation (Deeks, 2002). In view of the ease of interpretation, the use of RR may be prudent for use in meta-analyses pertaining to clinical interventions where outcomes are more likely to be interpreted and applied by clinicians rather than statisticians (Deeks, 2002). RR for assessing harm and OR provide comparable results in circumstances where events are uncommon, while RR assessing clinical benefit shows significantly increased heterogeneity when compared with the former two measures (Deeks, 2002). Empirical studies conducted by Deeks (2002) and

Engels *et al* (2000) demonstrated that RR and OR are comparable with regard to the consistency of results they provide, and RR are considered to be appropriate for use in assessments of both preventative and therapeutic interventions (Deeks, 2002). For these reasons it may have been preferable to use the RR summary statistic in the present work in view of the intent and context of its application. These have been subsequently computed (Appendix E) and show similar results as the previously described OR – this is not surprising in view of the rarity of events such as postoperative complications and mortality within the studies included.

Risk differences have been suggested as an alternative method of presenting summary data from binary statistics as these possess the benefit of presenting data in absolute terms, i.e. evaluating potential risk alongside potential benefit for patients at the individual level (Deeks, 2002). This application has clear merit for clinical practice where the individual is the focus. However, it has significant limitations in terms of producing inconsistent results and increased heterogeneity when compared with relative measures (Deeks, 2002; Engels *et al*., 2000).

5.1.3.2 Continuous Outcomes

WMD, in which the inverse of the variance of a given study is used as its weighting, was chosen for use with continuous outcomes in preference to the alternative option of standardised mean difference (SMD). This was possible in the present work as all continuous outcomes were measured uniformly across studies (that is, days). WMD is considered to be superior to SMD when outcomes are measured in the same units as it assigns weight to each study according to the sample size and precision, retains the original units of the outcome measure thus facilitating ease of interpretation, does not require adjustment for directional differences between scales, and avoids the assumption that variation detected is attributable to differences in measurement scales rather than true heterogeneity (Higgins and Green, 2006a).

5.2 Considerations in Interpretation of Results

5.2.1 Heterogeneity in Observed Results

While little to no heterogeneity was detected using either Q or I^2 statistics for the outcomes of mortality, anastomotic dehiscence, nasogastric tube reinsertion and pre-2000 subgroup analysis for both measures of resumption of bowel function, varying degrees of heterogeneity were detected for all other assessed outcomes. These ranged from mild heterogeneity, as in the pre-2000 subgroup analysis for postoperative complications (I^2= 15%), to extremely high levels, suggesting that close to 100% of the variation seen can be attributed to between-study variation. A striking example of this can be seen in the post-2000 subgroup analysis for passage of flatus where I^2 is 98.1% with a narrow range of 95% confidence intervals (95.18%-99.18%). In view of the detected heterogeneity, a random effects model of meta-analysis was utilised to accommodate the within- and between-study variation present (Huedo-Medina *et al*., 2006).

The presence of this degree of heterogeneity is of concern as both Q and I^2 statistics possess poor statistical power to detect heterogeneity in meta-analyses performed using small numbers of studies (Huedo-Medina *et al*., 2006; Ioannidis *et al*., 2007). There are conflicting reports in the literature about the number of studies required for these tests of heterogeneity to be adequately powered. While some authors report poor statistical power of the I^2 index in meta-analyses with less than 20 studies and/or an average sample size of under 80 (Huedo-Medina *et al*., 2006), others suggest around 15 studies in a meta-analysis to provide good power for both tests of heterogeneity (Ioannidis *et al*., 2007). The present work is at best adequately powered to detect heterogeneity and at worst underpowered. It is possible that the high degree of heterogeneity detected is actually an underestimate of the true heterogeneity present between studies in this meta-analysis. Should this be the case, combining some or many of the included studies for meta-analysis may be inappropriate due to inherent differences detected statistically, though not evident in the reporting of interventions or practices studied. In view of this, the data presented may be better suited to a regression approach or clustering procedure rather than meta-analysis which provides a single summary of results (Engels *et al*., 2000). However, this study did not pursue the regression approach due to the lack of relevant data on the potential explanatory variables available from the included studies.

A further implication of the heterogeneity detected is the questionability of whether obtaining point estimates is appropriate given the likelihood for between-study differences to be concealed under these circumstances (Brand and Kragt, 1992). For this reason forest plots have been presented to allow a visual evaluation of the results across studies and identification of differences which reduces the risk of differences in study outcomes being masked by the combined effect (Sutton and Higgins, 2008).

While some authors assert some degree of true heterogeneity is inevitable in a meta-analysis (Higgins and Green, 2006a; Sauerland and Seiler, 2005) there are a number of likely sources that can be identified in the current work that may contribute to the heterogeneity detected. Firstly, evolution of perioperative practices occurring over time and the cumulative effect of multiple changes being adopted as standard practice may contribute to true variation in results obtained. For example, multimodal analgesia and laparoscopic surgery have been increasingly adopted as standard practice over the last decade making the effect of early nutrition difficult or impossible to isolate from these other interventions. Secondly, a high degree of variation is an inherent part of surgical practice. For example, experienced surgeons have been shown to achieve better treatment outcomes than less experienced surgeons and surgical procedures are rarely able to be standardised for surgical randomised controlled trials (RCT) (Sauerland and Seiler, 2005). These unavoidable sources of heterogeneity will inevitably become incorporated into a meta-analysis dealing with surgical specialties. Thirdly, differences in the form of nutritional interventions have been provided (that is, tube feeding, oral fluids or solid diet) and resulting differences in the quantity of nutrition provided may also be a factor contributing to the heterogeneity detected. Finally, a visual assessment of the point estimates suggest that the Han-Guerts *et al* (2001; 2007) studies report dissimilar results to other included studies with regards to outcomes such as resumption of bowel function and LOS, and therefore may be responsible for a degree of the heterogeneity detected.

5.2.2 Publication Bias in the Present Work

Publication bias was assessed using multiple funnel plots. Log OR and WMD were plotted against sample size, precision and standard error for binary and continuous outcomes respectively. Irrespective of the choice of measure of the vertical axis, a visual assessment of the plots produced suggests the presence of publication bias for many outcomes assessed.

5.2.2.1 Horizontal Axis

Log ORs were selected as the statistic of choice for the horizontal axis of the funnel plots for binary outcomes as OR was the effect measure used throughout the meta-analysis. However, there are other reasons supporting the decision for use in the construction of funnel plots. Different effect measures have been shown to impact on asymmetry of funnel plots (Sterne and Egger, 2001). The greater between-study heterogeneity observed with risk differences compared with RR suggest against their use for constructing funnel plots in which real or erroneous heterogeneity will affect the shape of the plot produced (Sterne and Egger, 2001). It has been suggested that log OR are superior to log RRs for funnel plots by virtue of their constrained scale and consistency in shape irrespective of how the outcome is defined (Sterne and Egger, 2001).

WMD has been used to reflect the effect measure used within the meta-analysis for continuous variables. Little debate in or guidance from the literature could be located about the use of alternative methods for use in funnel plots with continuous data.

5.2.2.2 Vertical Axis

Asymmetry is clearly seen in all funnel plots where the effect size is plotted against sample size. Plotting effect size against sample size has been the traditional method for producing funnel plots for continuous variables (Begg and Mazumdar, 1994). However this method has been questioned regarding its use in binary outcomes, and is limited as 95% confidence intervals cannot be calculated when sample size is used on the vertical axis (Sterne and Egger, 2001). For binary outcomes, sample size is not considered a valid choice for the vertical axis of a funnel plot (Sterne and Egger, 2001).

Similarly, asymmetry is evident across all outcomes when plotted against effect size and precision (defined as the inverse of the standard error). Point distributions of the total complications, days to passage of flatus and LOS appear similar to those plotted against sample size, while other parameters show considerably different patterns of distribution. Use of precision along the vertical axis of funnel plots has been suggested as most useful on occasions where comparisons wish to be made between the outcomes of a large trial and a meta-analysis comprised of smaller studies, as this statistic clearly highlights differences between small and large study outcomes (Sterne and Egger, 2001).

Finally, log OR or WMD were plotted against the standard error for each assessed binary or continuous outcome respectively (see Appendix D). This method allowed for 95% confidence interval calculations to be performed and visually displayed on the funnel plot (Sterne and Egger, 2001). Of the four binary outcomes assessed, only the total complication rate demonstrated points falling outside of the confidence interval limits, indicating the need to reject the null hypothesis that publication bias was absent. The other three outcomes (mortality, anastomotic dehisence, nasogastric reinsertion rates) appeared symmetric on visual evaluation and thus support the acceptance of the null hypothesis based on the 95% confidence intervals. Funnel plots for the continuous variables all had points falling outside of the 95% confidence interval limits, thus supporting the rejection of the null hypothesis and suggesting the presence of publication bias. Use of the standard error is considered to be most appropriate choice for funnel plot construction as it produces the traditional funnel shape in the absence of publication bias and emphasises smaller studies where bias is expected to occur (Sterne and Egger, 2001).

5.2.2.3 Limitations to Assessment of Publication Bias in the Present Analysis

There are a number of possible factors contributing to the detection of publication bias in this meta-analysis. Firstly, both visual and statistical methods of assessing funnel plot asymmetry suffer limited statistical power when small study numbers are present (Duval and Tweedie, 2000; Sterne and Egger, 2001).This meta-analysis has only 15 studies that met inclusion criteria so valid assessment of publication bias is likely to be limited.

Secondly, a random effects model was applied to this meta-analysis as it better reflected the nature of the included studies. Although the random effects model has the benefit of compensating for a degree of unaccounted for between-study variation during the computation of point estimates, it may have amplified the presence of publication bias in funnel plot assessments (Greenland, 1994; Sterne and Egger, 2001). This occurs due to the assignment of relatively higher weight to smaller studies in which publication bias may be more prevalent in a random effects model (Greenland, 1994; Sterne and Egger, 2001). As yet, the literature does not contain suitable corrective or alternative measures to overcome this.

Thirdly, components of the inclusion and exclusion criteria for this meta-analysis will have contributed to the presence and subsequent detection of publication bias. The exclusion of unpublished studies and conference abstracts, along with the exclusion of non-English language studies will have increased the current work’s vulnerability to selection and publication bias from the outset (Egger and Smith, 1998). However, despite English language limits being set during literature searches, five non-English study abstracts were identified, two of which were RCTs. Despite being deemed to be relevant, attempts made to obtain full versions of the articles were unsuccessful. Subsequent searches for other non-English or unpublished RCTs that would meet the inclusion criteria yielded only two further potentially relevant studies – one published in Dutch (Beier-Holgersen and Boesby, 1998) located via a PubMed search, the other a conference abstract (Mulrooney *et al*, 2004) located from hand searching the reference list of the Andersen *et al* (2006) meta-analysis. Neither study could be located in full, nor did internet searches for authors of the Mulrooney *et al* (2004) abstract result in the location of any contact details to allow further enquiry. Therefore, the bias detected through funnel plot construction may be better described as location bias rather than publication bias *per se* (Egger *et al*., 1997b; Higgins and Green, 2006a).

Fourthly, heterogeneity was detected by both Q and I^2 statistics in a number of the outcomes assessed in the absence of any evident differences in methodology or interventions between studies. This would suggest there may be a significant amount of true heterogeneity present between studies included in this meta-analysis. This has implications for the interpretation of funnel plots as true heterogeneity will impact the shape of a funnel plot and limit the power to detect publication bias (Sterne and Egger, 2001; Tang and Liu, 2000).

5.3 Comparison of Results With Previously Published Meta-analyses

This meta-analysis supports the findings of the previous meta-analyses that traditional postoperative feeding practices confer no benefit in terms of outcomes following gastrointestinal resectional surgery (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). However, the results of the present meta-analysis are not as convincing as those previously reported which have demonstrated significant reductions in mortality, LOS and postoperative infection with early feeding (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). Significant increases in the occurrence of vomiting were also observed with early feeding interventions (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). There are a number of possible explanations for these differences and they are discussed below.

5.3.1 New Information From Studies Not Included in Previous Meta-analyses

Differences between the reported outcomes may arise from studies not included in the previous works. The current meta-analysis contained seven studies not included in the previous meta-analyses, representing three studies that do not appear to have been identified in previous literature searches (Han-Geurts *et al*., 2001; Lucha *et al*., 2005; Nessim *et al*., 1999), two that were identified but excluded from their analysis (Delaney *et al*., 2003; Ryan *et al*., 1981) and two further studies available following the publication of the 2006 meta-analyses (Han-Geurts *et al*., 2007; Zhou *et al*., 2006).

5.3.1.1 Outcome Differences in the Han-Geurts et al Studies (2001, 2007)

Of particular interest are the two Han-Guerts *et al* studies (2001; 2007) not included in any of the previously published meta-analyses. These appear to report outcomes different to the general trends reported in other studies, particularly with relation to return of bowel function and LOS. An examination of the published outcomes and the raw data obtained through correspondence with the authors highlight that an unusual number of extreme outliers are present in both papers, in each of the stated outcomes. These are outlined in Tables 5.1 and 5.2. Though reported as medians with ranges in both papers, an estimated and actual mean and standard deviation were computed for the 2001 and 2007 datasets respectively to allow point estimates to be calculated for inclusion in the meta-analysis. The implication of this in the presence of the extreme outliers results in the mean and standard deviation being falsely inflated thus providing results more discordant with other studies. The combination of the extreme outliers and the manipulation of the data into mean and standard deviations may adequately explain the differences observed. However, further investigations were undertaken in an attempt to elicit an explanation for the high number of outliers.

Table 5.1 - LOS data from Hans-Geurts *et al* (2001; 2007) papers

Outcomes as median (range) unless otherwise stated		Traditional feeding	Early feeding
Han-Guerts et al (2001)	Colonic surgery Colonic + vascular	12 (6-27) days 11 (6-34) days	15 (3-72) days 11 (3-72) days
Han-Guerts et al (2007)	Colonic surgery * Colonic + vascular	8 (5-160) days 17.5±4.2 days‡ 8 (5-160) days	9 (4-81) days 12±1.8 days‡ 9 (4-81) days

* Summary statistics computed from raw data provided by Dr Han-Guerts; ‡ Mean ± standard deviation

Table 5.2 – Numbers of Extreme outliers in Han-Guerts *et al* (2007) from raw data

	Traditional Feeding ("conventional diet")	Early Feeding ("free diet")
LOS	*n*=5 with LOS over 31 days	*n*=4 with LOS over 23 days
Days to passage of flatus	*n*=1 with >4 days	*n*=8 with >3 days
Days to first bowel motion	*n*=2 with >10 days; *n*=11 with first bowel motion on postoperative days 6 to 8.	*n*=2 with >9 days; *n*=9 with first bowel motion on postoperative days 6 to 8.

A thorough review of the methodology described in these papers was undertaken in order to elucidate an explanation for these differences, however no significant differences in any aspect of treatment were noted when compared with the other included papers. Initially, it was suspected that the presence of vascular patients among the study populations may explain the aberrations noted, yet little difference was found in outcomes when these were excluded from the 2007 dataset provided through correspondence with the authors. Although it is possible that the remaining vascular patients originating from the 2001 dataset may be contributing to this, it is unlikely as they represent only small proportion (2.9%) of the total pooled patient data.

Another possible contributing factor for the differences in the Han-Geurts *et al* (2001; 2007) study outcomes may be the unquantified nutritional consumption by patients in the early feeding groups. The early feeding protocol in these studies allowed patients to have solid diet from the first postoperative day and each individual patient was to determine what amount of food they desired to consume (Han-Geurts *et al*., 2001, 2007). These studies were included in the present work as it was rationalised that patients in any of the studies in which oral diet was provided as the early feeding intervention were self determining their intake. That is to say, unlike studies in which early feeding is provided via a feeding tube, investigators had no way of ensuring a specified caloric target was consumed orally. Conceivably, some patients in the early feeding group may have consumed little nutrition either by choice or due to symptoms, and may have had nutritional intakes not significantly different from patients receiving the traditional postoperative management. If this was the case, similar adverse outcomes originating from the same nutritional aetiology may have been observed by patients in both intervention arms. This may equally be true for any of the included studies in which oral feeding was commenced as the early nutritional intervention, although the effect may be amplified in these two studies as the onus for commencement and quantity of diet consumed was actively placed on the patients (Han-Geurts *et al*., 2001, 2007). Unfortunately, it is not possible to examine these potential differences further as no study documented the amount of oral nutritional intake ingested during the early postoperative period (Binderow *et al*., 1994; Delaney *et al*., 2003; Han-Geurts *et al*., 2001, 2007; Hartsell *et al*., 1997; Lucha *et al*., 2005; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Stewart *et al*., 1998; Zhou *et al*., 2006). Conversely, every study the provided nutrition via feeding tube reported this information (Beier-Holgersen and Boesby, 1996; Carr *et al*., 1996; Ryan *et al*., 1981; Sagar *et al*., 1979; Schroeder *et al*., 1991). It is possible that the lack of quantification of the nutrition consumed in the postoperative period may mask major differences (or similarities) in caloric or protein intake between intervention groups. We can only assume early feeding groups received more nutrition than the traditional groups in the absence of this information.

A review of the methodological quality of these studies was also undertaken as a possible explanation for these anomalies. The Han-Geurts *et al* studies (2001; 2007) demonstrated a relatively high quality when compared to others included in the analysis, thus it is possible that the results from these two Dutch studies may represent actual differences in outcomes contrary to those previously published with regard to early feeding. Conversely, it is possible that other unreported differences in postoperative practices exist in these studies and may be responsible for the comparative differences in outcomes observed. This is plausible, as of the 15 included studies, these two are the only ones that appear to contain extreme outliers.

5.3.2 Differences in Inclusion Criteria

The current meta-analysis has specified more rigid inclusion criteria with respect to nutritional factors: this is perhaps the most important difference between this meta-analysis and those previously published (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001).

5.3.2.1 Provision of Nutrition Proximal to the Anastomosis

Early feeding provided proximal to the anastomosis was required for inclusion in the present meta-analysis. Up to 12% of patients included in the previous meta-analyses were provided with early nutrition distal to the anastomosis (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). Fear of anastomotic dehiscence caused by food boluses, abdominal distension or vomiting from intolerance of oral diet has been anecdotally purported as a reason for avoidance of early feeding in gastrointestinal surgery (Casto *et al*., 2000). However, this appears to be based on flawed reasoning as ‘protecting the anastomosis’ overlooks that endogenous intestinal secretions of up to seven litres each day continue to be secreted and reabsorbed throughout the gastrointestinal tract irrespective of enteral intake in the post surgical period (Boron and Boulpaep, 2003). Furthermore, malnutrition and significant weight loss likely to be exacerbated by an extended delay in nutritional provision is recognised as a more significant risk factor in the development of anastomotic dehiscence (Kingham and Pachter, 2009). None of the individual studies included in or reviewed for this meta-analysis demonstrated an increase in anastomotic dehiscence with early feeding, regardless of the form in which it was delivered. Indeed, all meta-analyses to date suggest a trend toward decreased risk of this adverse outcome is associated with early feeding.

5.3.2.2 Nutritional Composition of Early Feeding

The provision of nutritionally significant foods or fluids provided within the first postoperative day was considered to be an important factor requisite for inclusion in this meta-analysis. Clear fluids are regularly chosen as the first oral intake postoperatively, irrespective of whether early feeding or traditional postoperative management is being provided (Hancock *et al*., 2002). However there is little basis for this dietary provision as it provides negligible nutritional value and patients have been shown to tolerate the early introduction of solid diet without significant adverse outcomes following a range of surgical procedures, including upper gastrointestinal surgery (Hancock *et al*., 2002; Jeffery *et al*., 1996; Lassen *et al*., 2008). Furthermore, malnutrition is common in elective gastrointestinal surgery patients (Ward, 2003; Windsor and Hill, 1988). Malnutrition is independently associated with poor outcomes such as delayed wound healing, development of postoperative complications and mortality in surgical patients (Clark *et al*, 2000; Gallagher-Allred *et al*., 1996; Huckleberry, 2004; Ward, 2003; Windsor and Hill, 1988). The catabolic effects of the stress response induced by surgery are well recognised (Brunicardi, 2005; Kehlet, 2006), as is the ability of adequate nutrition to attenuate the magnitude of the inflammatory responses (Grimble, 2008) and nitrogen losses sustained the postoperative period (Delaney *et al*., 1977; Hindmarsh and Clark, 1973). For this reason, early provision of nutritionally significant foods and fluids has a greater potential to positively influence outcomes than indiscriminate provision of food and fluids within the early postoperative period. Nutrition most likely modulates the body’s response to surgical stress and reduces the caloric deficit in the days immediately following surgery, thus reducing the degree of nutritional depletion experienced postoperatively.

The present meta-analysis excluded studies in which immune-enhancing formulas such as Impact® (Nestle Nutrition, Minneapolis, USA) were provided as the early feeding intervention. This decision was based on reports in the literature suggesting that owing to the conditionally essential nature of the amino acid arginine in surgical patients, provision of this amino acid in pharmacological quantities may improve postoperative outcomes such as reduced infective complications and LOS (Zheng *et al*., 2007). All previously published meta-analyses on this topic include a large study by Heslin *et al* (1997) that utilises an immune-enhancing enteral formula provided distal to the anastomosis as the early feeding intervention. This study represents 21% of the patients included in the meta-analysis in the 2001 analysis, and 16% of the total number of patients in the subsequent meta-analyses (Andersen *et al*., 2006; Lewis *et al*., 2008; Lewis *et al*., 2001). In view of the large proportion of patients included and the potential of these specialised nutritional products to impact postoperative outcomes it is felt the inclusion of this study potentially confounds the results of the previously published meta-analyses. This is particularly so given that Heslin *et al* (1997) is also the largest of the included studies (*n*=197) and, as such, will be the most heavily weighted owing to the use of the fixed effect model in these meta-analyses (Borenstein *et al*., 2007). As a result of this, the Heslin *et al* (1997) study has the greatest potential to influence the summary estimates of the existing meta-analyses.

5.4 Limitations of Meta-analysis

There are a number of limitations contained in this meta-analysis that may affect the outcomes obtained. These include the presence of bias, studies of poor methodological quality and assumptions made: these are outlined below.

5.4.1 Assumptions Made

A number of assumptions have been made throughout the preparation of this meta-analysis that may affect the outcomes obtained. Firstly, in an attempt to standardise the differences in reporting between articles, several authors were contacted for clarification of reported trials or additional information within their published data. In cases where no response was returned assumptions relating to the interpretation of various aspects of their published reports were made, such as the composition of the fluid diets reported (Delaney *et al*., 2003; Hartsell *et al*., 1997; Zhou *et al*., 2006), or discrepancies in the reporting within the paper (Stewart *et al*., 1998). For these reasons, although every attempt has been made to ensure analysed studies meet inclusion criteria and that other data are accurate, there may still be unknown reporting errors affecting the results obtained.

5.4.2 Methodological Quality

The studies included in this meta-analysis consistently yielded poor scores for methodological quality using the Jadad scoring system (Jadad *et al*., 1996; Moher *et al*., 1998). Out of a possible score of five, a mean score of 1.9 was achieved, with a maximum score of three. Limitations of applying traditional methods of assessing methodological quality to nutrition and surgical studies due to the often impossible task of blinding for obvious interventions are acknowledged. However, there should be no impediment to reporting withdrawals or method of randomisation. Increased emphasis on improving the quality of reporting in clinical trials in the medical literature has occurred in recent years, including initiatives such as the Consolidated Standards for Reporting of Randomised Trials (CONSORT) statement (Begg *et al*., 1996). Despite this, no difference was seen in the Jadad score in the mean pre- and post-2000 methodology scores (pre-2000 2.0, post-2000 1.8, p=0.9). As there is some suggestion that studies of low methodological quality may yield inflated effect sizes (Moher *et al*., 1998) the low methodological scores have possible ramifications for the interpretations of outcomes of this meta-analysis which favour early feeding.

A number of alternatives to methodological scoring have been proposed in an attempt to overcome the above issues including stratification, regression analyses, and multiple sensitivity analyses (Greenland, 1994; Olkin, 1994). All these methods aim to more clearly demonstrate possible relationships between variables and outcomes of the study with a view to understanding which of the factors impact the issue under investigation. Irrespective of the limitations of the traditional tools for assessing methodological quality, the proposed alternative methods may be more useful exploratory applications for nutrition and surgical trials given the difficulties of applying traditional methodological tools to these areas of research. However, the reporting of the required covariates to allow for such an analysis, along with the prerequisite number of studies to allow for valid analysis, will likely remain a limitation of applying these tools.

5.4.3 Bias in Subgroup Analyses

5.4.3.1 Statistical Issues in the Subgroup Analyses

Studies included in this meta-analysis were stratified for year of publication to control for the developments in perioperative care. As noted in 5.1.2, for most outcomes observed results more strongly favoured early feeding in the pre-2000 subgroup than in the post-2000 studies. While statistical power conferred by greater numbers may contribute to this observation, this may not be case for outcomes. For example, in the case of total complications (k=10 studies involving 608 patients pre-2000 versus k=5 studies involving 632 patients post-2000), no such explanation can be proposed for the days to passage of flatus (k=2 studies involving 112 patients pre-2000 versus k=2 involving 408 patients post-2000). In this particular example the small number of individuals patients involved in the pre-2000 subgroup may have resulted in a Type II error due to the small effect size and poor statistical power (De Veaux *et al*., 2006).

A further explanation may lie in the heterogeneity between subgroups. In every outcome measure assessed, less heterogeneity as measured by Q statistic and I^2 index was seen in the pre-2000 subgroup analyses when compared with those of the post-2000 groups. However, similar issues of statistical power as described above may nevertheless be responsible for these findings. Possible sources of the detected heterogeneity have been described in section 5.2.1.

The selection of dates from which to stratify data also has the potential to affect the outcome of the subgroup analyses. Several options were considered before the decision was made to use the year 2000 as the point of separation. Firstly, stratification by decade was discarded due to the disproportionate distribution of studies across the four decades covered (k=1 in 1970s, k=1 in 1980s, k=8 in 1990s, k=5 in 2000s) and the implications of this for statistical power.

Secondly, the year 1995 was considered as this was the point in time when multimodal enhanced recovery after surgery programs first appeared in the literature (Kehlet, 2008). If non-nutritional elements of perioperative care with the potential to improve postoperative outcomes were introduced following this time, 1995 would make an appropriate separation point. This cut off was also abandoned due to the uneven distribution of studies (pre-1995 k=4, post-1995 k=11) and subsequent implications for statistical power. In view of the documented poor adoption of these multimodal programs as a whole (Kehlet, 2006; Kehlet *et al*., 2006; Kehlet and Wilmore, 2008) it stands to reason that there would be little statistical or practical benefit to the use of this separation point.

Finally, the year 2000 was proposed and adopted as the point of separation. Although this choice does not eliminate the concerns with uneven study distribution within subgroups (pre-2000 k=10, post-2000 k=5) the final decision was made upon consultation with an experienced gastrointestinal surgeon (Professor M A Memon) who felt that as an arbitrary cut off point the year 2000 should provide an adequate distinction between adopted surgical and perioperative practices reported in the included studies.

The appropriateness of conducting a subgroup analysis as part of the current work can be questioned due to the implications for statistical power resulting from having fewer than ten studies available for each subgroup (Higgins and Green, 2006a). Similar limitations would also exist for other investigations of heterogeneity, including meta-regression (Higgins and Green, 2006a). Likewise, the decision to investigate differences using subgroup analysis was made *post hoc* following a consideration of the pooled results, so represent a further bias to the analysis (Higgins and Green, 2006a).

5.4.1.2 Changes in Early Feeding Practices Affecting Subgroup Analyses

Changes in perioperative practices are likely to play a role in explaining the differences seen between stratified subgroups. Consideration of nutritional factors alone demonstrates a positive progression toward providing more physiologically normal nutrition support in the early postoperative period. Sagar *et al* (1979) and Ryan *et al* (1981) commenced early feeding conservatively by the present standards through providing diluted elemental formula into the jejunum, which over time progressed to the provision of standard polymeric feed products into the duodenum or jejunum (Beier-Holgersen and Boesby, 1996; Carr *et al*., 1996; Schroeder *et al*., 1991), oral fluids (Hartsell *et al*., 1997; Zhou *et al*., 2006), and finally full diet within 24-hours postoperatively (Aiko *et al*., 2005; Binderow *et al*., 1994; Delaney *et al*., 2003; Han-Geurts *et al*., 2001, 2007; Lucha *et al*., 2005; Nessim *et al*., 1999; Ortiz *et al*., 1996b; Stewart *et al*., 1998).

In addition to the previously discussed issues regarding the unquantifiable variation in oral nutritional intake in the post-2000 subgroup, there is a further question as to whether dietary texture has any effect on tolerance or postoperative outcomes. Currently, investigations into the impact of dietary texture or composition of early nutrition provided proximal to the anastomosis are limited in the literature. Of those that do compare proximal dietary intake and tube feeding distal to the anastomosis, beneficial outcomes have been reported with oral feeding. A recently published multi-centred RCT comparing the outcomes of early jejunal feeding with the early introduction of solid oral intake in elective upper gastrointestinal surgery patients suggested that comparable outcomes were noted between groups, and that orally fed patients had shorter LOS (Lassen *et al*., 2008). Though not receiving nutritionally significant nutritional intake until the third postoperative day, similar findings were observed in a pilot study in which patients received proximal oral feeding following distal gastrectomy for gastric malignancy (Hur *et al*., 2009).

5.4.1.3 Changes to Other Aspects of Perioperative Care Affecting Subgroup Analyses

Further to changes in nutritional provision, other aspects of surgical and perioperative care may impact the results obtained from this meta-analysis. Changes to anaesthetic and analgesia prescribing practices have trended toward opioid-sparing options. This is believed to reduce nausea, vomiting, sedation, and development of post operative ileus (Kehlet and Wilmore, 2008) and thus facilitate the earlier tolerance of enteral nutrition. The adoption of minimally invasive surgery in preference to open procedures has shortened postoperative recovery times through reducing the size of the surgical incision when compared with traditional laparotomy procedures (Kehlet, 1999). In addition to reducing postoperative pain and the cascade of inflammatory responses that lead to catabolism (Chachkhiani *et al*., 2005; Kehlet, 1999; Kehlet and Wilmore, 2008), these changes facilitate early mobilisation which has been associated with improved circulation and reduction in postoperative respiratory and thromboembolic complications (Mynster *et al*., 1996).

While included studies were not specifically reported as multimodal approaches to post surgical management, the increasing adoption of the elements of these programs over time are likely to influence the results of this meta-analysis. It is therefore feasible that they may be responsible for some degree of the beneficial results being attributed in this analysis to early feeding, particularly with a cumulative effect of multiple strategies being embraced. This may be particularly true of the more recent studies in which these philosophies are being more widely accepted as standard practice.

5.5 Future Directions

5.5.1 Elucidation of Quantity of Nutritional Provision Required to Improve Patient Outcomes

It has been an underlying hypothesis of this meta-analysis that the benefit obtained from early enteral nutrition interventions is a result of the provision of calories, protein and micronutrients. These in turn induce anabolism while maintaining gut barrier function, thus facilitating healing and recovery earlier than occurs through traditional postoperative nutritional management. However, studies suggest that trophic effects of enteral nutrition still occur when nutritional provision is less than adequate (Zaloga *et al*., 1992). Hence there may be a threshold of nutritional provision that is therapeutic and results in beneficial outcomes despite being considerably less than the patient's complete nutritional requirements. Indications from the critical care literature suggests 50 to 65% of goal nutritional requirements may be required to obtain outcomes, such as reduced intestinal permeability or more rapid return of cognitive function (Martindale *et al*., 2009). No comparable data is currently available for surgical patients. Such a relationship between nutrition provision and postoperative outcomes could potentially be elucidated from estimations of caloric and protein intakes from patients in early versus traditional feeding trials when collected in conjunction with anthropometric data. This information may provide answers to clinical questions such as "Is there a minimum level of caloric and/or protein intake required to reduce LOS or total complications?", "Does full diet versus nutrient-rich fluid provision in the early period postoperatively result in a greater risk of anastomotic dehiscence?", or "What effect does early versus traditional feeding have on anthropometric outcomes, such as weight and lean body mass in the postoperative period, and how does this affect outcomes and recovery?". This information has the potential to revolutionise perioperative nutritional practice and enhance outcomes for patients and the institutions in which they are treated.

Unfortunately, the absence of food consumption records that would allow an estimation of caloric and protein intake in the early postoperative period is a major omission in the clinical trials investigating early oral feeding, and probably reflects the limited multidisciplinary collaboration occurring in the implementation of these trials. It is critical that both of these issues be addressed in future studies. Collection of this information would not only assist in broadening our understanding of the interaction between nutritional intake and outcomes reported, but is required to help quantify absolute differences in nutritional intake between intervention groups, as this is poorly characterised in studies to date.

5.5.2 Further Development of Meta-analysis Methodology and Statistical Methods

Meta-analysis is highly regarded in clinical fields as a robust methodology that has important applications to clinical decision making and as such is placed at the pinnacle of the hierarchy of evidence within the concept of evidence-based practice (Evans, 2003). However, as this meta-analysis has demonstrated, there currently exist some limitations to its application to both surgical and nutrition research. These limitations include: (i) that the number of studies available for consideration are generally small, (ii) detection is limited by what is readily available in the public or academic domain, and (iii) acquisition of potentially relevant studies not published in English is often difficult or impossible. International registers of RCTs, such as the Cochrane Controlled Trials Register, in theory, may alleviate many sources of selection and publication bias and overcome some of issues outlined above. However, obstacles still exist such as how to enforce involvement in such registers, timely registration of trials, and dissemination of results from completed trials (Egger and Smith, 1998).

Similarly, as medical meta-analysis is a relatively new application of a well established statistical method, it follows that the statistical procedures used to produce a medical meta-analysis are also evolving to better meet the unique conditions presented by studies of clinical practice (Sauerland and Seiler, 2005). Examples of areas where more statistical research and modelling are required as highlighted by the current work include: (i) improved methods to detect publication bias, particularly when random effects models of meta-analysis are applied, and where the meta-analysis is comprised of a small number of studies, (ii) development of tests for heterogeneity with improved sensitivity to detect between-study variation in circumstances where small numbers of studies are involved, (iii) empirical investigation into the effect of assuming normal distribution during the application of random effects model of meta-analysis, (iv) guidance on investigation of heterogeneity in the circumstances where a small number of studies make subgroup analysis, meta-regression and other methods of sensitivity analysis difficult or invalid, and (v) further investigation on the effect of methodological quality on the influence of effect size in areas of surgery and nutrition.

Notwithstanding the identified limitations, meta-analysis continues to provide a strong basis for clinical decision making when it is conducted using robust methodology and statistical methods appropriately matched to the nature of the interventions being investigated (Egger and Smith, 1997; Ng *et al*., 2006). The benefits applied to clinical practice by meta-analysis will only be strengthened as statistical methods are further developed to better reflect the needs of the areas to which they are applied, and as the research infrastructure is made more supportive of producing high quality, reliable medical meta-analyses.

5.5.3 Implications for Clinical Education and Continuing Professional Development

Health professionals generally receive a rudimentary education in research methodology and statistics during their clinical training. For this reason they are unlikely to be aware of the limitations and implications of many subtleties contained within the evidence-based literature they read and are expected to apply to clinical practice, such as recognising if the underlying conditions for producing a reliable meta-analysis have been met. Some authors address this issue by advising against meta-analysis automatically being regarded as level I evidence in view of the limitations of meta-analytical procedures when applied to many clinical settings at the present time (Sauerland and Seiler, 2005). However, in the interest of providing high quality clinical practice, supporting clinicians to develop a deeper understanding of these issues in order to apply critical appraisal to meta-analyses and other clinical trials conducted and promoted within their specialty must be considered a more desirable option. Therefore, further emphasis should be placed on the inclusion of applied statistics and research methodology into clinical training programs and continuing professional development courses to facilitate a safe and informed application of evidence-based practice.

Chapter 6 Conclusions

The present work supports the claims of the growing body of evidence that early postoperative feeding in elective gastrointestinal resectional surgery patients is safe and beneficial. Results demonstrate significant reductions in total postoperative complications in early feeding interventions when compared with traditional practice, while trends toward reduction in mortality, anastomotic dehiscence, length of hospital stay, development of nausea and vomiting, and resumption of bowel function were also observed. The most adverse event reported with early feeding was non-significantly increased, trend in the need for nasogastric tube reinsertion. This may be considered a surrogate measure for reporting the presence of nausea and/or vomiting in the later studies. However, these results need to be considered in terms of the inherit limitations of the meta-analysis. Specifically, the relatively small number of studies included, largely unexplained heterogeneity detected between studies involving several of the outcomes assessed, and indications of the presence of bias as evidenced by funnel plot asymmetry.

The stated objectives of the present work have been met by

- Limiting the inclusion of studies to those that compare traditional nil-by-mouth nutritional management to the provision of nutritionally adequate diet or tube feeding within 24-hours of surgery, delivered proximal to the surgical anastomosis;
- Using a thorough literature search methodology that located eligible studies not appearing in previous meta-analyses on this topic; and
- Applying the random effects model of meta-analysis in acknowledgement of the lack of uniformity of clinical practice within the interventions and studies being pooled and assessed.

Several applications to clinical practice are highlighted by the present work. Firstly, as the results provide further support for the safety of and benefit conferred by early feeding interventions following elective gastrointestinal surgery, early feeding should be promoted and adopted as standard practice by surgeons and their professional associations. This practice should also be supported by hospital policies in the institutions in which elective gastrointestinal surgical procedures are performed; a surgical culture that embraces and supports early feeding in the context of the promotion evidence-based practice should be encouraged and commended.

Secondly, it highlights some limitations in the application of evidence-based practice when clinicians possess a limited understanding of statistics and research methodology. There are many areas where bias and methodological limitations may influence the results obtained from a meta-analysis of clinical interventions, and thus subsequent conclusions drawn. Without an appreciation of these issues, clinicians may inadvertently adopt misleading or poor quality recommendations believing themselves to be implementing evidence-based practice. Therefore, care is required with the blanket promotion of meta-analysis as the best source of clinical evidence and clinicians must receive a more thorough education in statistical methods and research methodology during their training and continuing professional development.

They should be encouraged and expected to critically evaluate any research they intend to apply to clinical practice to ensure it is appropriate for their client group and to recognise when the methodological processes undertaken have been sufficiently robust to justify the adoption of the practices recommended therein. The importance of these knowledge and skills should be reinforced and further developed throughout a clinician's career to facilitate a sound application of evidence-based practice as well as to advance clinical research. This should be supported by the policies of institutions employing clinicians as well as their professional associations and registration boards.

Furthermore, this meta-analysis has highlighted the need for multi-disciplinary collaboration in trials investigating early versus traditional postoperative nutritional management to facilitate improved reporting of nutritional consumption and anthropometric outcomes. It has also highlighted areas requiring further research and modelling to better match meta-analysis methodology and statistical procedures with the clinical contexts to which they are now being applied. These include the development of methods to deal more robustly with small study numbers, and the development of more sensitive methods to detect heterogeneity and bias.

6.1 Recommendations

The recommendations and findings from the current work can be summarised as:

- The provision of nutritionally adequate food or enteral feeds within 24-hours of elective gastrointestinal resectional surgery is safe and reduces the risk of postoperative complications and should be adopted as standard practice;
- Institutional policies and surgical professional associations should support and promote the adoption of early feeding practices in view of the weight of supporting evidence;
- Clinicians require a greater degree of training in statistics and research methodology – the foundations of this should be provided in entry-level training and should be continued to be developed throughout their careers to facilitate their capacity to apply evidence-based practice and to contribute to clinical research;
- Future studies that investigate the effect of early versus traditional postoperative feeding practices must take a more multi-disciplinary approach and include data collection of caloric and nutritional intake, as this is a major omission in all studies to date; and
- Further modelling of the statistical procedures that are used in producing a medical meta-analysis are required to ensure these are sufficiently developed to deal with the unique conditions posed by interventions undertaken a clinical environment.

References

Agresti, A. (1996). *An introduction to Categorical Data Analysis*: Wiley & Sons.

Aihara, H., Kawamura, Y. J., and Konishi, F. (2003). Reduced medical costs achieved after elective oncological colorectal surgery by early feeding and fewer scheduled examinations. *J Gastroenterol* **38**, 747-750.

Aiko, S., Yoshizumi, Y., Sugiura, Y.*, et al.* (2001). Beneficial effects of immediate enteral nutrition after esophageal cancer surgery. *Surg Today* **31**, 971-978.

Aiko, S., Yoshizumi, Y., Tsuwano, S., Shimanouchi, M., Sugiura, Y., and Maehara, T. (2005). The effects of immediate enteral feeding with a formula containing high levels of omega-3 fatty acids in patients after surgery for esophageal cancer. *JPEN J Parenter Enteral Nutr* **29**, 141-147.

Alves, A., Panis, Y., and Chipponi, J. (2004). Should early feeding be permitted following elective colorectal resection? *Ann Chir* **129**, 94-95.

Andersen, H. K., Lewis, S. J., and Thomas, S. (2006). Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. *Cochrane Database Syst Rev*, CD004080.

Anderson, A. D., McNaught, C. E., MacFie, J., Tring, I., Barker, P., and Mitchell, C. J. (2003). Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg* **90**, 1497-1504.

Arthur, J., Jones, H., Anderson, J., Walsh, C., and Makin, C. A. (2004). Early feeding after large bowel resection results in earlier discharge. *Annals of the Royal College of Surgeons of England* **86**, 481-482.

Ashrafi, A. N., and Pochin, R. (2007). Gs25p postoperative nil by mouth - simply a surgical dogma or scientifically sound practrice? *ANZ J Surg* **77**, 1:A31.

Bahn, L. (2006). Serum Proteins as Markers of Nutrition: What are We Treating? *Practical Gastroenterology*, 46-64.

Balk, E. M., Bonis, P. A., Moskowitz, H.*, et al.* (2002). Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA* **287**, 2973-2982.

Basse, L., Raskov, H. H., Hjort Jakobsen, D.*, et al.* (2002). Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *Br J Surg* **89**, 446-453.

Basse, L., Thorbol, J. E., Lossl, K., and Kehlet, H. (2004). Colonic surgery with accelerated rehabilitation or conventional care. *Dis Colon Rectum* **47**, 271-277; discussion 277-278.

Beattie, A. H., Prach, A. T., Baxter, J. P., and Pennington, C. R. (2000). A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut* **46**, 813-818.

Begg, C., Cho, M., Eastwood, S., *et al.* (1996). Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* **276**, 637-639.

Begg, C. B., and Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics* **50**, 1088-1101.

Beier-Holgersen, R., and Boesby, S. (1996). Influence of postoperative enteral nutrition on postsurgical infections. *Gut* **39**, 833-835.

Beier-Holgersen, R., and Boesby, S. (1998). [Effect of early postoperative enteral nutrition on postoperative infections]. *Ugeskr Laeger* **160**, 3223-3226.

Bickel, A., Shtamler, B., and Mizrahi, S. (1992). Early oral feeding following removal of nasogastric tube in gastrointestinal operations. A randomized prospective study. *Arch Surg* **127**, 287-289; discussion 289.

Binderow, S. R., Cohen, S. M., Wexner, S. D., and Nogueras, J. J. (1994). Must early postoperative oral intake be limited to laparoscopy? *Dis Colon Rectum* **37**, 584-589.

Binderow, S. R., Cohen, S. M., Wexner, S. D., Schmitt, S. L., Nogueras, J. J., and Jagelman, D. G. (1993). Must early postoperative oral intake be limited to laparoscopy? *Int J Colorectal Dis* **8**, 230.

Bisgaard, T., and Kehlet, H. (2002). Early oral feeding after elective abdominal surgery--what are the issues? *Nutrition* **18**, 944-948.

Borenstein, M., Hedges, L., and Rothstein, H. (2007). Meta-analysis: Fixed Effect vs Random Effects. www.meta-analysis.com Access date: 18/10/2008.

Boron, W. F., and Boulpaep, E. L. (eds) (2003). *Medical Physiology*. Philadelphia: Saunders.

Braga, M., Gianotti, L., Nespoli, L., Radaelli, G., and Di Carlo, V. (2002). Nutritional approach in malnourished surgical patients: a prospective randomized study. *Arch Surg* **137**, 174-180.

Braga, M., Gianotti, L., Radaelli, G., *et al.* (1999). Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. *Arch Surg* **134**, 428-433.

Brand, R., and Kragt, H. (1992). Importance of trends in the interpretation of an overall odds ratio in the meta-analysis of clinical trials. *Stat Med* **11**, 2077-2082.

Brockwell, S. E., and Gordon, I. R. (2001). A comparison of statistical methods for meta-analysis. *Stat Med* **20**, 825-840.

Browning, L., Denehy, L., and Scholes, R. L. (2007). The quantity of early upright mobilisation performed following upper abdominal surgery is low: an observational study. *Aust J Physiother* **53**, 47-52.

Brunicardi, F. C. (ed) (2005). *Schwartz's Principles of Surgery*, 8th edition. New York: McGraw-Hill.

Buchmann, P., Bischofberger, U., De Lorenzi, D., and Christen, D. (1998). [Early postoperative nutrition after laparoscopic and open colorectal resection]. *Swiss Surg* **4**, 146-155.

Bufo, A. J., Feldman, S., Daniels, G. A., and Lieberman, R. C. (1994). Early postoperative feeding. *Dis Colon Rectum* **37**, 1260-1265.

Carr, C. S., Ling, K. D., Boulos, P., and Singer, M. (1996). Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. *BMJ* **312**, 869-871.

Casto, C. J., Krammer, J., and Drake, J. (2000). Postoperative feeding: a clinical review. *Obstet Gynecol Surv* **55**, 571-573.

Chachkhiani, I., Gurlich, R., Maruna, P., Frasko, R., and Lindner, J. (2005). The postoperative stress response and its reflection in cytokine network and leptin plasma levels. *Physiol Res* **54**, 279-285.

Champe, P. C., and Harvey, R. A. (1994). *Biochemistry*, 2nd edition. Philadelphia: J. B. Lippincott Company.

Charoenkwan, K., Phillipson, G., and Vutyavanich, T. (2007). Early versus delayed (traditional) oral fluids and food for reducing complications after major abdominal gynaecologic surgery. *Cochrane Database Syst Rev*, CD004508.

Chiarelli, A., Enzi, G., Casadei, A., Baggio, B., Valerio, A., and Mazzoleni, F. (1990). Very early nutrition supplementation in burned patients. *Am J Clin Nutr* **51**, 1035-1039.

Choi, J., and O'Connell, T. X. (1996). Safe and effective early postoperative feeding and hospital discharge after open colon resection. *Am Surg* **62**, 853-856.

Clark, M. A., Plank, L. D., and Hill, G. L. (2000). Wound healing associated with severe surgical illness. *World J Surg* **24**, 648-654.

Cochran, W. G. (1954). The combination of estimates from different experiments. *Biometrics* **10**, 101-129.

Correia, M. I., and da Silva, R. G. (2004). The impact of early nutrition on metabolic response and postoperative ileus. *Curr Opin Clin Nutr Metab Care* **7**, 577-583.

Cutillo, G., Maneschi, F., Franchi, M., Giannice, R., Scambia, G., and Benedetti-Panici, P. (1999). Early feeding compared with nasogastric decompression after major oncologic gynecologic surgery: a randomized study. *Obstet Gynecol* **93**, 41-45.

Dalmia, S., Keh, C., and Patel, R. (2001). Early Postoperative Feeding After Elective Colorectal Resection and Postoperative Stay. *Colorectal Dis* **3** 88.

Davey Smith, G., and Egger, M. (1998). Meta-analysis. Unresolved issues and future developments. *BMJ* **316**, 221-225.

Davey Smith, G., Egger, M., and Phillips, A. N. (1997). Meta-analysis. Beyond the grand mean? *BMJ* **315**, 1610-1614.

De-Souza, D. A., and Greene, L. J. (2005). Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. *Crit Care Med* **33**, 1125-1135.

de Aguilar-Nascimento, J. E., and Goelzer, J. (2002). [Early feeding after intestinal anastomoses: risks or benefits?]. *Rev Assoc Med Bras* **48**, 348-352.

De Veaux, R. D., Velleman, P. F., and Bock, D. E. (2006). *Intro Stats*, 2nd edition. Boston: Pearson Addison Wesley.

Deeks, J. J. (2002). Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med* **21**, 1575-1600.

Deeks, J. J., Macaskill, P., and Irwig, L. (2005). The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol* **58**, 882-893.

Deitch, E. A. (2002). Bacterial translocation or lymphatic drainage of toxic products from the gut: what is important in human beings? *Surgery* **131**, 241-244.

Delaney, C. P., Zutshi, M., Senagore, A. J., Remzi, F. H., Hammel, J., and Fazio, V. W. (2003). Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum* **46**, 851-859.

Delaney, H. M., Carnevale, J., Garvey, J. W., and Moss, C. M. (1977). Postoperative nutritional support using needle catheter feeding jejunostomy. *Annals of Surgery* **186**, 165 - 170.

Denehy, L. (2008). Physiotherapy and thoracic surgery: thinking beyond usual practice. *Physiother Res Int* **13**, 69-74.

DerSimonian, R., and Laird, N. (1986). Meta-analysis in clinical trials. *Control Clin Trials* **7**, 177-188.

Desborough, J. P. (2000). The stress response to trauma and surgery. *Br J Anaesth* **85**, 109-117.

Detry, R., Ciccarelli, O., Komlan, A., and Claeys, N. (1999). Early feeding after colorectal surgery. Preliminary results. *Acta Chir Belg* **99**, 292-294.

Di Fronzo, L. A., Cymerman, J., and O'Connell, T. X. (1999). Factors affecting early postoperative feeding following elective open colon resection. *Arch Surg* **134**, 941-945; discussion 945-946.

Dickersin, K., Min, Y. I., and Meinert, C. L. (1992). Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. *JAMA* **267**, 374-378.

DiFronzo, L. A., Yamin, N., Patel, K., and O'Connell, T. X. (2003). Benefits of early feeding and early hospital discharge in elderly patients undergoing open colon resection. *J Am Coll Surg* **197**, 747-752.

Donohoo, E., Harvey, A., Jarvis, J., and Keen, S. (2003). Kapanol. In *MIMS online*: Health Communication Network.

Duval, S., and Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455-463.

Easterbrook, P. J., Berlin, J. A., Gopalan, R., and Matthews, D. R. (1991). Publication bias in clinical research. *Lancet* **337**, 867-872.

Egbert, L. D., Battit, G. E., Welch, C. E., and Bartlett, M. K. (1964). Reduction of Postoperative Pain by Encouragement and Instruction of Patients. A Study of Doctor-Patient Rapport. *N Engl J Med* **270**, 825-827.

Egger, M., and Smith, G. D. (1997). Meta-Analysis. Potentials and promise. *BMJ* **315**, 1371-1374.

Egger, M., and Smith, G. D. (1998). Bias in location and selection of studies. *BMJ* **316**, 61-66.

Egger, M., Smith, G. D., and Phillips, A. N. (1997a). Meta-analysis: principles and procedures. *BMJ* **315**, 1533-1537.

Egger, M., Smith, G. D., Schneider, M., and Minder, C. (1997b). Bias in meta-analysis detected by a simple, graphical test. *Br Med J* **315**, 629-634.

Emerson, J. D., Burdick, E., Hoaglin, D. C., Mosteller, F., and Chalmers, T. C. (1990). An empirical study of the possible relation of treatment differences to quality scores in controlled randomized clinical trials. *Control Clin Trials* **11**, 339-352.

Engels, E. A., Schmid, C. H., Terrin, N., Olkin, I., and Lau, J. (2000). Heterogeneity and statistical significance in meta-analysis: an empirical study of 125 meta-analyses. *Stat Med* **19**, 1707-1728.

Evans, C., Galustian, C., Kumar, D.*, et al.* (2008). Impact of surgery on immunologic function: comparison between minimally invasive techniques and conventional laparotomy for surgical resection of colorectal tumors. *Am J Surg*.

Evans, D. (2003). Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. *J Clin Nurs* **12**, 77-84.

Eyer, S. D., Micon, L. T., Konstantinides, F. N.*, et al.* (1993). Early enteral feeding does not attenuate metabolic response after blunt trauma. *J Trauma* **34**, 639-643; discussion 643-634.

Fanning, J., and Andrews, S. (2001). Early postoperative feeding after major gynecologic surgery: evidence-based scientific medicine. *Am J Obstet Gynecol* **185**, 1-4.

Feo, C. V. (2008). R: early post operative feeding. E. Osland (ed).

Feo, C. V., Romanini, B., Sortini, D., *et al.* (2004). Early oral feeding after colorectal resection: a randomized controlled study. *ANZ J Surg* **74**, 298-301.

Fukushima, R., Kawamura, Y. J., Saito, H., *et al.* (1996). Interleukin-6 and stress hormone responses after uncomplicated gasless laparoscopic-assisted and open sigmoid colectomy. *Dis Colon Rectum* **39**, S29-34.

Gabor, S., Renner, H., Matzi, V., *et al.* (2005). Early enteral feeding compared with parenteral nutrition after oesophageal or oesophagogastric resection and reconstruction. *Br J Nutr* **93**, 509-513.

Galbraith, R. F. (1988). A note of graphical presentation of estimted odds ratios from several clinical trials. *Stat Med* **7**, 889-894.

Gallagher-Allred, C. R., Voss, A. C., Finn, S. C., and McCamish, M. A. (1996). Malnutrition and clinical outcomes: the case for medical nutrition therapy. *J Am Diet Assoc* **96**, 361-366, 369; quiz 367-368.

Gatt, M., Anderson, A. D., Reddy, B. S., Hayward-Sampson, P., Tring, I. C., and MacFie, J. (2005). Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg* **92**, 1354-1362.

Gatt, M., and MacFie, J. (2007). Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery (Br J Surg 2007; 94: 555-561). *Br J Surg* **94**, 1044-1045.

Grahm, T. W., Zadrozny, D. B., and Harrington, T. (1989). The benefits of early jejunal hyperalimentation in the head-injured patient. *Neurosurgery* **25**, 729-735.

Greenland, S. (1994). Invited commentary: a critical look at some popular meta-analytic methods. *Am J Epidemiol* **140**, 290-296.

Grimble, R. F. (2008). Basics in clinical nutrition: Main cytokines and their effect during injury and sepsis. *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism* **3**, e289-292.

Guys Hospital (1761). Surgical Diet. In *Old Operating Theatre, Guys Hospital*, P1010313 (ed). London.

Han-Geurts, I. J., Hop, W. C., Kok, N. F., Lim, A., Brouwer, K. J., and Jeekel, J. (2007). Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery. *Br J Surg* **94**, 555-561.

Han-Geurts, I. J., Jeekel, J., Tilanus, H. W., and Brouwer, K. J. (2001). Randomized clinical trial of patient-controlled versus fixed regimen feeding after elective abdominal surgery. *Br J Surg* **88**, 1578-1582.

Hancock, S., Cresci, G., and Martindale, R. (2002). The clear liquid diet: when is it appropriate? *Curr Gastroenterol Rep* **4**, 324-331.

Harper, C. M., and Lyles, Y. M. (1988). Physiology and complications of bed rest. *J Am Geriatr Soc* **36**, 1047-1054.

Hartsell, P. A., Frazee, R. C., Harrison, J. B., and Smith, R. W. (1997). Early postoperative feeding after elective colorectal surgery. *Arch Surg* **132**, 518-520; discussion 520-511.

Hedberg, A. M., Lairson, D. R., Aday, L. A.*, et al.* (1999). Economic implications of an early postoperative enteral feeding protocol. *J Am Diet Assoc* **99**, 802-807.

Hedges, L. V., and Olkin, I. (1985). *Statistical methods for meta analysis*. Orlando: Academic Press.

Henriksen, M. G., Hansen, H. V., and Hessov, I. (2002a). Early oral nutrition after elective colorectal surgery: influence of balanced analgesia and enforced mobilization. *Nutrition* **18**, 263-267.

Henriksen, M. G., Hansen, H. V., Jensen, M. B., Jespersen, T. W., Rodt, S. A., and Hessov, I. (1998). Importance of balanced analgesia, early oral feeding and enforced mobilization for the postoperative convalescence after colorectal surgery. *JPEN J Parenter Enteral Nutr* **22**, S8.

Henriksen, M. G., Jensen, M. B., Hansen, H. V., Jespersen, T. W., and Hessov, I. (2002b). Enforced mobilization, early oral feeding, and balanced analgesia improve convalescence after colorectal surgery. *Nutrition* **18**, 147-152.

Heslin, M. J., Latkany, L., Leung, D.*, et al.* (1997). A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. *Ann Surg* **226**, 567-577; discussion 577-580.

Higgins, J. P., and Green, S. (eds) (2006a). *Analysing and Presenting Results. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. Section 8. In: The Cochrane Library, Issue 4* Chichester: John Wiley & Sons, Ltd.

Higgins, J. P., and Green, S. (eds) (2006b). *Appendix 8a Considerations and recommendations for figures in Cochrane reviews: Graphs of statistical data. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Appendices*. Chichester, UK: John Wiley & Sons Ltd.

Higgins, J. P. T., and Green, S. (eds) (2006c). *Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006] In: The Cochrane Library, Issue 4*, 4.2.6 edition. Chichester: John Wiley & Sons, Ltd.

Higgins, J. P. T., and Green, S. (eds) (2008). *Cochrane Handbook for Systematic Review of Interventions, Version 5.0.1 [Updated September 2008]*: The Cochrane Collaboration.
Higgins, J. P. T., and Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* **21**, 1539-1558.

Hindmarsh, J. T., and Clark, R. G. (1973). The effects of intravenous and intraduodenal feeding on nitrogen balance after surgery. *British Journal of Surgery* **60**, 589-594.

Hiratsuka, K., Tsunoda, A., Shibusawa, M., and Kusano, M. (2003). Early postoperative feeding following colon cancer surgery: a randomized controlled trial. *Japanese Journal of Gastroenterological Surgery* **36**, 1370-1378.

Hochwald, S. N., Harrison, L. E., Heslin, M. J., Burt, M. E., and Brennan, M. F. (1997). Early postoperative enteral feeding improves whole body protein kinetics in upper gastrointestinal cancer patients. *Am J Surg* **174**, 325-330.

Holte, K., and Kehlet, H. (2002). Epidural anaesthesia and analgesia - effects on surgical stress responses and implications for postoperative nutrition. *Clin Nutr* **21**, 199-206.

Holte, K., Sharrock, N. E., and Kehlet, H. (2002). Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth* **89**, 622-632.

Hornik, K. (2008). R: A language and environment for statistical computing. Vienna: Foundation for Statistical computing.

Howard, L., and Ashley, C. (2003). Nutrition in the perioperative patient. *Annu Rev Nutr* **23**, 263-282.

Hozo, S. P., Djulbegovic, B., and Hozo, I. (2005). Estimating the mean and variance from the median, range and size of a sample. *BMC Medical Research Methodology* **5**, 13.

Huckleberry, Y. (2004). Nutritional support and the surgical patient. *Am J Health Syst Pharm* **61**, 671-682; quiz 683-674.

Huedo-Medina, T. B., Sanchez-Meca, J., Marin-Martinez, F., and Botella, J. (2006). Assessing heterogeneity in meta analysis: statistic or index? . *The American Psychological Association* **11**, 193 - 206.

Hur, H., Si, Y., Kang, W. K., Kim, W., and Jeon, H. M. (2009). Effects of Early Oral Feeding on Surgical Outcomes and Recovery After Curative Surgery for Gastric Cancer: Pilot Study Results. *World J Surg*.

Ioannidis, J. P., and Lau, J. (1998). Can quality of clinical trials and meta-analyses be quantified? *Lancet* **352**, 590-591.

Ioannidis, J. P., Patsopoulos, N. A., and Evangelou, E. (2007). Uncertainty in heterogeneity estimates in meta-analyses. *BMJ* **335**, 914-916.

Jadad, A. R., Moore, A., Carroll, D., *et al.* (1996). Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Controlled Clinical Trials* **17**, 1-12.

Jeffery, K. M., Harkins, B., Cresci, G. A., and Martindale, R. G. (1996). The clear liquid diet is no longer a necessity in the routine postoperative management of surgical patients. *Am Surg* **62**, 167-170.

Jenkins, M., Gottschlich, M., Alexander, J. W., and Warden, G. D. (1989). Effect of immediate enteral feeding on the hypermetabolic response following severe burn injury. *J Parenter Enteral Nutr* **13**, 12S.

Kasparek, M. S., Mueller, M. H., Glatzle, J.*, et al.* (2004). Postoperative colonic motility increases after early food intake in patients undergoing colorectal surgery. *Surgery* **136**, 1019-1027.

Kawamura, Y. J., Uchida, H., Watanabe, T., and Nagawa, H. (2000). Early feeding after oncological colorectal surgery in Japanese patients. *J Gastroenterol* **35**, 524-527.

Kehlet, H. (1999). Surgical stress response: does endoscopic surgery confer an advantage? *World J Surg* **23**, 801-807.

Kehlet, H. (2006). Labat lecture 2005: surgical stress and postoperative outcome-from here to where? *Reg Anesth Pain Med* **31**, 47-52.

Kehlet, H. (2008). Fast-track colorectal surgery. *Lancet* **371**, 791-793.

Kehlet, H., Buchler, M., Beart, R., and Williamson, R. (2004). Nasogastric intubation and early nutrition following colorectal surgery in Europe. *Br J Surg* **91**, 149.

Kehlet, H., Buchler, M. W., Beart, R. W., Jr., Billingham, R. P., and Williamson, R. (2006). Care after colonic operation--is it evidence-based? Results from a multinational survey in Europe and the United States. *J Am Coll Surg* **202**, 45-54.

Kehlet, H., and Dahl, J. B. (2003). Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* **362**, 1921-1928.

Kehlet, H., and Wilmore, D. W. (2002). Multimodal strategies to improve surgical outcome. *Am J Surg* **183**, 630-641.

Kehlet, H., and Wilmore, D. W. (2008). Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* **248**, 189-198.

Khoo, C. K., Vickery, C. J., Forsyth, N., Vinall, N. S., and Eyre-Brook, I. A. (2007). A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. *Ann Surg* **245**, 867-872.

King, P. M., Blazeby, J. M., Ewings, P.*, et al.* (2006). The influence of an enhanced recovery programme on clinical outcomes, costs and quality of life after surgery for colorectal cancer. *Colorectal Dis* **8**, 506-513.

Kingham, T. P., and Pachter, H. L. (2009). Colonic Anastomotic Leak: Risk Factors, Diagnosis, and Treatment. *Journal of the American College of Surgeons* **208**, 269-278.

Kiyama, T., Onda, M., Tokunaga, A., Yoshiyuki, T., and Barbul, A. (2000). Effect of early postoperative feeding on the healing of colonic anastomoses in the presence of intra-abdominal sepsis in rats. *Dis Colon Rectum* **43**, S54-58.

Klek, S., Kulig, J., Sierzega, M., *et al.* (2008). Standard and immunomodulating enteral nutrition in patients after extended gastrointestinal surgery--a prospective, randomized, controlled clinical trial. *Clin Nutr* **27**, 504-512.

Kurz, A. (2008). Thermal care in the perioperative period. *Best Pract Res Clin Anaesthesiol* **22**, 39-62.

Lassen, K., Kjaeve, J., Fetveit, T., *et al.* (2008). Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. *Ann Surg* **247**, 721-729.

Lassen, K., and Revhaug, A. (2006). Early oral nutrition after major upper gastrointestinal surgery: why not? *Curr Opin Clin Nutr Metab Care* **9**, 613-617.

Lewis, S. J., Andersen, H. K., and Thomas, S. (2008). Early Enteral Nutrition Within 24 h of Intestinal Surgery Versus Later Commencement of Feeding: A Systematic review and Meta-analysis. *J Gastrointest Surg*.

Lewis, S. J., Egger, M., Sylvester, P. A., and Thomas, S. (2001). Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *BMJ* **323**, 773-776.

Ljungqvist, O., Nygren, J., and Thorell, A. (1998). Preoperative carbohydrates instead of overnight fasting reduces hospital stay following elective surgery [abstract]. *Clin Nutr* **17**, 10.

Ljungqvist, O., Nygren, J., and Thorell, A. (2000). Insulin resistance and elective surgery. *Surgery* **128**, 757-760.

Lobo, D. N., Williams, R. N., Welch, N. T., *et al.* (2006). Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled, double-blind study. *Clin Nutr* **25**, 716-726.

Lucha, P. A., Jr., Butler, R., Plichta, J., and Francis, M. (2005). The economic impact of early enteral feeding in gastrointestinal surgery: a prospective survey of 51 consecutive patients. *Am Surg* **71**, 187-190.

Lumley, T. (2008). The rmeta Package Version 2.14.

MacKay, G., Ihedioha, U., McConnachie, A., Serpell, M., Molloy, R., and O'Dwyer, P. (2007). Laparoscopic colonic resection in fast-track patients does not enhance short-term recovery after elective surgery. *Colorectal Dis* **9**, 368-372.

Mackay, M. R., Ellis, E., and Johnston, C. (2005). Randomised clinical trial of physiotherapy after open abdominal surgery in high risk patients. *Aust J Physiother* **51**, 151-159.

Malhotra, A., Mathur, A. K., and Gupta, S. (2004). Early enteral nutrition after surgical treatment of gut perforations: a prospective randomised study. *J Postgrad Med* **50**, 102-106.

Martindale, R. G., McClave, S. A., Vanek, V. W., *et al.* (2009). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. *Crit Care Med* **37**, 1757-1761.

Matarese, L. E., and Gottschlich, M. M. (eds) (1998). *Contemporary Nutrition Support Pracitce: A Clinical Guide*, Second edition. Philadelphia: Saunders.

Memon, M. A., Memon, B., Memon, M. I., and Donohue, J. H. (2002). The uses and abuses of drains in abdominal surgery. *Hosp Med* **63**, 282-288.

Mochizuki, H., Trocki, O., Dominioni, L., Brackett, K. A., Joffe, S. N., and Alexander, J. W. (1984). Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. *Ann Surg* **200**, 297-310.

Moher, D., Cook, D. J., Eastwood, S., Olkin, I., Rennie, D., and Stroup, D. F. (1999). Improving the quality of reports of meta-analyses of randomised controled trials: the QUOROM statement. *The Lancet* **354**, 1896-1900.

Moher, D., Pham, B., Jones, A., *et al.* (1998). Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* **352**, 609-613.

Montejo, J. C., Grau, T., Acosta, J., *et al.* (2002). Multicenter, prospective, randomized, single-blind study comparing the efficacy and gastrointestinal complications of early jejunal feeding with early gastric feeding in critically ill patients. *Crit Care Med* **30**, 796-800.

Mullally, T. (1947). After care - post-operative. In *British Surgical Practice*, S. E. R. Claring, and J. P. Ross (eds), 134. London: Butterworth & Co.

Muller, E. A. (1970). Influence of training and of inactivity on muscle strength. *Arch Phys Med Rehabil* **51**, 449-462.

Mulrooney, L. J., Bagley, J. S., Wilkinson, J. A., Keltry, C., Coker, A. O., and Jacob, G. (2004). Nasojejunal feeding does not improve clinical outcomes and is poorly tolerated following colorectal surgery. In *BAPEN Abstract Book*, OC 16: BAPEN.

Mynster, T., Jensen, L. M., Jensen, F. G., Kehlet, H., and Rosenberg, J. (1996). The effect of posture on late postoperative oxygenation. *Anaesthesia* **51**, 225-227.

National Health and Medical Council (2005). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: Australian Government. http://www.nhmrc.gov.au/guidelines/_files/levels_grades05.pdf Access date: 16/9/2009.

Nelson, R., Edwards, S., and Tse, B. (2007). Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database Syst Rev*, CD004929.

Nessim, A., Wexner, S. D., Agachan, F., *et al.* (1999). Is bowel confinement necessary after anorectal reconstructive surgery? A prospective, randomized, surgeon-blinded trial. *Dis Colon Rectum* **42**, 16-23.

Ng, T. T., McGory, M. L., Ko, C. Y., and Maggard, M. A. (2006). Meta-analysis in surgery: methods and limitations. *Arch Surg* **141**, 1125-1130; discussion 1131.

Ng, W. Q., and Neill, J. (2006). Evidence for early oral feeding of patients after elective open colorectal surgery: a literature review. *J Clin Nurs* **15**, 696-709.

Noblett, S. E., Watson, D. S., Huong, H., Davison, B., Hainsworth, P. J., and Horgan, A. F. (2006). Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. *Colorectal Dis* **8**, 563-569.

Nygren, J., Soop, M., Thorell, A., Efendic, S., Nair, K. S., and Ljungqvist, O. (1998). Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clin Nutr* **17**, 65-71.

Nygren, J., Thorell, A., and Ljungqvist, O. (2003). New developments facilitating nutritional intake after gastrointestinal surgery. *Curr Opin Clin Nutr Metab Care* **6**, 593-597.

Olkin, I. (1994). Re: "A critical look at some popular meta-analytic methods". *Am J Epidemiol* **140**, 297-299; discussion 300-291.

Ortiz, H. (2008). Re: early postoperative feeding. E. Osland (ed).

Ortiz, H., Armendariz, P., and Yarnoz, C. (1996a). Early postoperative feeding after elective colorectal surgery is not a benefit unique to laparoscopy-assisted procedures. *Int J Colorectal Dis* **11**, 246-249.

Ortiz, H., Armendariz, P., and Yarnoz, C. (1996b). Is early postoperative feeding feasible in elective colon and rectal surgery? *Int J Colorectal Dis* **11**, 119-121.

Ortiz, H., Armendariz, P., Yarnoz, C., De Miguel, M., Chocarro, C., and Ciga, M. A. (1995). Colorectal surgery: a claim for earlier oral feeding. *Br J Surg* **82**, 33.

Parker, M. C. (1997). Early postoperative feeding after elective colorectal surgery is not a benefit unique to laparoscopy-assisted procedures. *Int J Colorectal Dis* **12**, 51-52.

Pearl, M. L. (1997). Early postoperative feeding in gynecologic oncology patients undergoing intra-abdominal surgery. *Gynecol Oncol* **66**, 345.

Pearl, M. L., Frandina, M., Mahler, L., Valea, F. A., Di Silvestro, P. A., and Chalas, E. (2002). A Randomized Controlled Trial of a Regular Diet as the First Meal in Gynecologic Oncology Patients Undergoing Intraabdominal Surgery. *Obstet Gynecol* **100**, 230-234.

Pearl, M. L., Valea, F. A., Fischer, M., Mahler, L., and Chalas, E. (1998). A randomized controlled trial of early postoperative feeding in gynecologic oncology patients undergoing intra-abdominal surgery. *Obstet Gynecol* **92**, 94-97.

Pearl, M. L., Valea, F. A., Fischer, M., Mahler, L., and Chalas, E. (1999). A Randomized Controlled Trial of Early Postoperative Feeding in Gynecologic Oncology Patients Undergoing Intra-Abdominal Surgery. *Journal of Urology* **161**, 370.

Petrelli, N. J., Cheng, C., Driscoll, D., and Rodriguez-Bigas, M. A. (2001). Early postoperative oral feeding after colectomy: an analysis of factors that may predict failure. *Ann Surg Oncol* **8**, 796-800.

Petrie, A., and Sabin, C. (2000). *Medical Statistics at a Glance*. Oxford: Blackwell Science.

Raue, W., Haase, O., Junghans, T., Scharfenberg, M., Muller, J. M., and Schwenk, W. (2004). 'Fast-track' multimodal rehabilitation program improves outcome after laparoscopic sigmoidectomy: a controlled prospective evaluation. *Surg Endosc* **18**, 1463-1468.

Reissman, P., Teoh, T. A., Cohen, S. M., Weiss, E. G., Nogueras, J. J., and Wexner, S. D. (1995). Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. *Ann Surg* **222**, 73-77.

Rodgers, A., Walker, N., Schug, S.*, et al.* (2000). Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* **321**, 1493.

Rothstein, H. (2008). Publication bias as a threat to meta-analytic results. *Journal of Experimental Criminology* **4**, 61-81.

Rowlands, B. J., and Gardiner, K. R. (1998). Nutritional modulation of gut inflammation. *Proc Nutr Soc* **57**, 395-401.

Ryan, J. A., Jr., Page, C. P., and Babcock, L. (1981). Early postoperative jejunal feeding of elemental diet in gastrointestinal surgery. *Am Surg* **47**, 393-403.

Sagar, S., Harland, P., and Shields, R. (1979). Early postoperative feeding with elemental diet. *Br Med J* **1**, 293-295.

Saito, H., Trocki, O., Alexander, J. W., Kopcha, R., Heyd, T., and Joffe, S. N. (1987). The effect of route of nutrient administration on the nutritional state, catabolic hormone secretion, and gut mucosal integrity after burn injury. *JPEN J Parenter Enteral Nutr* **11**, 1-7.

Sands, D. R., and Wexner, S. D. (1999). Nasogastric tubes and dietary advancement after laparoscopic and open colorectal surgery. *Nutrition* **15**, 347-350.

Sauerland, S., and Seiler, C. M. (2005). Role of systematic reviews and meta-analysis in evidence-based medicine. *World J Surg* **29**, 582-587.

Schilder, J. M., Hurteau, J. A., Look, K. Y.*, et al.* (1997). A prospective controlled trial of early postoperative oral intake following major abdominal gynecologic surgery. *Gynecol Oncol* **67**, 235-240.

Schroeder, D., Gillanders, L., Mahr, K., and Hill, G. L. (1991). Effects of immediate postoperative enteral nutrition on body composition, muscle function, and wound healing. *JPEN J Parenter Enteral Nutr* **15**, 376-383.

Schulz, K. F., Chalmers, I., Hayes, R. J., and Altman, D. G. (1995). Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* **273**, 408-412.

Schwenk, W., Bohm, B., Haase, O., Junghans, T., and Muller, J. M. (1998). Laparoscopic versus conventional colorectal resection: a prospective randomised study of postoperative ileus and early postoperative feeding. *Langenbecks Arch Surg* **383**, 49-55.

Seenu, V., and Goel, A. K. (1995). Early oral feeding after elective colorectal surgery: is it safe. *Trop Gastroenterol* **16**, 72-73.

Senkal, M., Mumme, A., Eickhoff, U.*, et al.* (1997). Early postoperative enteral immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. *Crit Care Med* **25**, 1489-1496.

Sessler, D. I. (1997). Mild perioperative hypothermia. *N Engl J Med* **336**, 1730-1737.

Seven, H., Calis, A. B., and Turgut, S. (2003). A randomized controlled trial of early oral feeding in laryngectomized patients. *Laryngoscope* **113**, 1076-1079.

Sheldon, T. A. (1999). Systematic reviews and meta-analyses: the value for surgery. *Br J Surg*
86, 977-978.

Silk, D. B., and Gow, N. M. (2001). Postoperative starvation after gastrointestinal surgery. Early feeding is beneficial. *BMJ* **323**, 761-762.

Singh, G., Ram, R. P., and Khanna, S. K. (1998). Early postoperative enteral feeding in patients with nontraumatic intestinal perforation and peritonitis. *J Am Coll Surg* **187**, 142-146.

Smedley, F., Bowling, T., James, M.*, et al.* (2004). Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *Br J Surg* **91**, 983-990.

Smith, G. D., and Egger, M. (1998). Incommunicable knowledge? Interpreting and applying the results of clinical trials and meta-analyses. *J Clin Epidemiol* **51**, 289-295.

Sobotka, L., Allison, S. P., Furst, P., Meier, R., Pertkiewicz, M., and Soeters, P. (eds) (2004). *Basics in Clinical Nutrition*, 3rd edition. Prague: Galen.

Soop, M. (2003). Effects of perioperative nutrition on insulin effect in postoperative metabolism. Stockholm: Karolinska Institutet.

Soop, M., Nygren, J., and Hammarqvist, F. (2001). Preoperative oral carbohydrate treatment attenuates postoperative whole body nitrogen losses and hepatic insulin resistance. *Clin Nutr* **21**, 50.

Steed, H. L., Capstick, V., Flood, C., Schepansky, A., Schulz, J., and Mayes, D. C. (2002). A randomized controlled trial of early versus "traditional" postoperative oral intake after major abdominal gynecologic surgery. *Am J Obstet Gynecol* **186**, 861-865.

Stephen, A. E., and Berger, D. L. (2003). Shortened length of stay and hospital cost reduction with implementation of an accelerated clinical care pathway after elective colon resection. *Surgery* **133**, 277-282.

Stern, J. M., and Simes, R. J. (1997). Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ* **315**, 640-645.

Sterne, J. A., and Egger, M. (2001). Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* **54**, 1046-1055.

Sterne, J. A., Gavaghan, D., and Egger, M. (2000). Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* **53**, 1119-1129.

Stewart, B. T., Woods, R. J., Collopy, B. T., Fink, R. J., Mackay, J. R., and Keck, J. O. (1998). Early feeding after elective open colorectal resections: a prospective randomized trial. *Aust N Z J Surg* **68**, 125-128.

Studley, H. O. (1936). Percentage of weight loss: A basic indicator fo surgical risk in patients with chronic peptic ulcer. *JAMA* **106**, 458.

Suehiro, T., Matsumata, T., Shikada, Y., and Sugimachi, K. (2004). Accelerated rehabilitation with early postoperative oral feeding following gastrectomy. *Hepatogastroenterology* **51**, 1852-1855.

Sutton, A. J., Abrams, K. R., Jones, D. R., Sheldon, T. A., and Song, F. (2000). *Methods for Meta-analysis in Medical Research*: John Wiley.

Sutton, A. J., and Higgins, J. P. (2008). Recent developments in meta-analysis. *Stat Med* **27**, 625-650.

Tang, J. L., and Liu, J. L. Y. (2000). Misleading funnel plot detection of bias in meta-analysis. *J Clin Epidermiol* **53**, 477-484.

Terrin, N., Schmid, C. H., Lau, J., and Olkin, I. (2003). Adjusting for publication bias in the presence of heterogeneity. *Stat Med* **22**, 2113-2126.

The Cochrane Collaboration (2002). Module 15: Publicaiton bias. Open Learning Package: The Cochrane Collabortation.

Todd, A. H. (1915). *A Practical Handbook of Surgical After-Treatment*. London: Edward Arnold.

Torosian, M. H. (1999). Perioperative nutrition support for patients undergoing gastrointestinal surgery: critical analysis and recommendations. *World J Surg* **23**, 565-569.

Tsunoda, A., Shibusawa, M., Takata, M., Hiratsuka, K., Shida, K., and Kusano, M. (2005). Early oral feeding should be resumed following the resolution of gastric ileus. *Hepatogastroenterology* **52**, 775-779.

Urbach, D. R., Kennedy, E. D., and Cohen, M. M. (1999). Colon and rectal anastomoses do not require routine drainage: a systematic review and meta-analysis. *Ann Surg* **229**, 174-180.

Veterans Affairs Total Parenteral Nutrition Cooperative Study Group (1991). Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. *N Engl J Med* **325**, 525-532.

Wakely, C. P. G., and Hunter, J. B. (1940). *Rose and Careless' Manual of Surgery*. London: Bailliere, Tindall & Cox.

Ward, N. (2003). Nutrition support to patients undergoing gastrointestinal surgery. *Nutr J* **2**, 18.

Watters, J. M., Kirkpatrick, S. M., Norris, S. B., Shamji, F. M., and Wells, G. A. (1997). Immediate postoperative enteral feeding results in impaired respiratory mechanics and decreased mobility. *Ann Surg* **226**, 369-377; discussion 377-380.

Way, L. W. (ed) (1988). *Current Surgical Diagnosis and Treatment*. Sydney: Prentice/Hall International.

Wexner, S. D. (1996). "Is early postoperative feeding feasible in elective colon and rectal surgery?" *Int J Colorectal Dis* **11**, 303.

Wilmore, D. W. (2002). From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. *Ann Surg* **236**, 643-648.

Wind, J., Polle, S. W., Fung, K. J., Dejong, C. H. C., and Bemelman, W. A. (2006a). Enhanced recovery after surgery ('fast track') programs in colonic surgery: a systematic review. *European Journal of Gastroenterology and Hepatology* **18**, A43.

Wind, J., Polle, S. W., Fung Kon Jin, P. H., *et al.* (2006b). Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* **93**, 800-809.

Windsor, J. A., and Hill, G. L. (1988). Weight loss with physiologic impairment. A basic indicator of surgical risk. *Ann Surg* **207**, 290-296.

Wischmeyer, P. E. (2005). Can glutamine turn off the motor that drives systemic inflammation? *Crit Care Med* **33**, 1175-1178.

Wu, L., and Griffiths, P. (2005). Early postoperative feeding and abdominal gynaecological surgery. *Br J Nurs* **14**, 42-46.

Yuill, K. A., Richardson, R. A., Davidson, H. I., Garden, O. J., and Parks, R. W. (2005). The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial. *Clin Nutr* **24**, 32-37.

Zaloga, G. P., Black, K. W., and Prielipp, R. (1992). Effect of rate of enteral nutrient supply on gut mass. *JPEN J Parenter Enteral Nutr* **16**, 39-42.

Zheng, Y., Li, F., Qi, B., *et al.* (2007). Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. *Asia Pac J Clin Nutr* **16 Suppl 1**, 253-257.

Zhou, T., Wu, X. T., Zhou, Y. J., Huang, X., Fan, W., and Li, Y. C. (2006). Early removing gastrointestinal decompression and early oral feeding improve patients' rehabilitation after colorectostomy. *World J Gastroenterol* **12**, 2459-2463.

Zonca, P., Stigler, J., Maly, T., Neoral, C., Hajek, M., and Stiglerova, S. (2008). Do we really apply fast-track surgery? *Bratisl Lek Listy* **109**, 61-65.

Appendix A - Search Terms Utilised During the Literature Search

Pubmed - http://www.ncbi.nlm.nih.gov/pubmed/

Searched 12/11/2007, 14/11/2007

(RCT and EARLY FEEDING and COLORECTAL)

(RCT and EARLY FEEDING and GASTRIC)

(RCT and EARLY FEEDING and UPPER GI)

(RCT and EARLY FEEDING and POSTOPERATIVE)

(EARLY and POSTOPERATIVE and RANDOMIS/ZED and FEED*)

(PROSPECTIVE and RANDOMIS/ZED and ORAL and POSTOPERATIVE and FEED*)

(EARLY and ORAL and FEED* and SURGERY) + limits added 'randomized control trial; meta-analysis; ages 19-80+'

(EARLY and POSTOPERATIVE and NUTRITION) + limits added 'randomized control trial; 'ages 19-80+'

Trials Cochrane Search

Searched 15/11/07

(EARLY and ORAL and FEEDING)

(EARLY and POSTOPERATIVE and FEEDING)

Cochrane Library

Searched 15/11/07

(EARLY ORAL FEEDING)

(EARLY FEEDING)

(EARLY FEEDING and POSTOPERATIVE)

Google Scholar - http://scholar.google.com.au/

Searched 14/11/07

(EARLY POSTOPERATIVE FEEDING)

Ovid@journals

Searched 15/11/07

(EARLY POSTOPERATIVE FEEDING)

EBSCOhost – CINAHL and MEDLINE

Searched 15/11/07

Conditions: Advanced Search; Boolean searches applied; Expander 'Apply related words'

Limits: Publication type 'clinical trial'; Age group 'Adult 19-44 years', 'Middle aged 45-64 years', 'Aged 65+ years' +/- Special Interests 'Perioperative care', 'Nutrition'

(EARLY FEEDING and COLORECTAL)

(EARLY FEEDING and GASTRIC)

(EARLY FEEDING and GASTRO*)

(EARLY POSTOPERATIVE and NUTRITION)

(EARLY and POSTOPERATIVE and RANDOMI?ED and FEEDING)

(PROSPECTIVE and RANDOMI?ED and ORAL and POSTOPERATIVE and FEEDING)

(EARLY and ORAL and FEED* and SURGERY)

Appendix B – Data Extraction Form

Inclusion Assessment Criteria – early feeding meta-analysis

Paper/Author:

INCLUDE EXCLUDE

1. **Study methodology** Randomised control trial? Method of randomisation? Blinding? Documents/discusses withdrawals from study? →Jadad score? Assesses early vs NBM (traditional) feeding as primary end points?	
1. **Study population** Type of surgery performed? Elective/emergency Open/laparoscopic Surgical procedures Age of subjects?	
1. **Early feeding intervention** Nutrition provided in first 24hr (day after surgery/D1 post op)? Clear fluids? Free fluids? Diet? Enteral feed product? Standard Immune modulating Semi/Elemental Nutrition provided distal to the anastomosis?	
1. **Traditional feeding intervention** Intervention provided to traditional group (control)	
1. **Additional Comments?**	

Appendix C – Raw Data from Excel Spreadsheets

Table C.1 - Basic Study Information

Author	Year / Country	Nutrition route		Post op (<24hrs)	D1 post op (24hrs)	D2 post op (48hrs)	n = early	n = control
Sagar *et al*	1979 / England	jejunal	Flexical (elemental)	NBM	diluted tube feed	FS tube feed	15	15
Ryan *et al*	1981 / USA	jejunal	Vivonex	diluted tube feed	diluted tube feed	diluted tube feed	7	7
Schroeder *et al*	1991 / New Zealand	jejunal or duodenal	Osmolite	FS tube feed	FS tube feed	FS tube feed	16	16
Binderow *et al*	1993 / USA	oral		NBM	regular diet	regular diet	32	32
Beier-Holgersen *et al*	1996 / Denmark	duodenal	Nutridrink	FS tube feed	FS tube feed	FS tube feed	30	30
Carr *et al*	1996 / England	jejunal	Fresibun	FS tube feed	FS tube feed	FS tube feed	14	14
Ortiz *et al*	1996 / Spain	oral		clear fluids	regular diet	regular diet	93	95
Hartsell *et al*	1997 / USA	oral		NBM	full fluids	regular diet	29	29
Nessim *et al*	1997 / USA	oral		regular diet	regular diet	regular diet	27	27
Stewart *et al*	1998 / Australia	oral		free fluids	regular diet	regular diet	40	40
Hans-Geurts *et al*	2001 / The Netherlands	oral		? regular diet	? regular diet	? regular diet	56	49
Delaney *et al*	2003 / USA	oral		fluids (?type)	regular diet PM/fluid diet AM	regular diet	31	33
Lucha *et al*	2005 / USA	oral		regular diet	regular diet	regular diet	26	25
Zhou *et al*	2006 / China	oral		NBM	liquid fibreless diet	liquid fibreless diet	161	155
Hans-Geurts *et al*	2007 / The Netherlands	oral		regular diet	regular diet	regular diet	46	50
							623	617

NBM=Nil by Mouth
FS=Full strength

2007 Han-Guerts data uses data from correspondence with Dr Han. 51 patients in intestinal control group, 1 with missing data omitted for results provided

Table C.2 - Jadad Score

Author	Year / Country	n =		Jadad total	Randomisation	Blinding	Withdrawals/drop outs
		early	control	total = 5	out of 2	out of 2	0-1
Sagar *et al*	1979 / England	15	15	1	1	0	0
Ryan *et al*	1981 / USA	7	7	2	1	0	1
Schroeder *et al*	1991 / New Zealand	16	16	2	1	0	1
Binderow *et al*	1993 / USA	32	32	1	1	0	0
Beier-Holgersen *et al*	1996 / Denmark	30	30	2	1	1	0
Carr *et al*	1996 / England	14	14	3	2	0	1
Ortiz *et al*	1996 / Spain	93	95	2	1	0	1
Hartsell *et al*	1997 / USA	29	29	1	1	0	0
Nessim *et al*	1997 / USA	27	27	3	2	0	0
Stewart *et al*	1998 / Australia	40	40	3	2	0	1
Hans-Geurts *et al*	2001 / The Netherlands	56	49	2	2	0	0
Delaney *et al*	2003 / USA	31	33	2	2	0	0
Lucha *et al*	2005 / USA	26	25	1	1	0	0
Zhou *et al*	2006 / China	161	155	1	1	0	0
Hans-Geurts *et al*	2007 / The Netherlands	46	50	3	2	0	1
		623	**617**	**29**	**21**	**1**	**6**
				1.9	**1.4**	**0.1**	**0.4**

Table C.3 - Mortality

Author	Year / Country	n = early	n = control	Mortality early	Mortality control
Sagar *et al*	1979 / England	15	15	0	0
Ryan *et al*	1981 / USA	7	7	0	0
Schroeder *et al*	1991 / New Zealand	16	16	0	0
Binderow *et al*	1993 / USA	32	32	0	0
Beier-Holgersen *et al*	1996 / Denmark	30	30	2	4
Carr *et al*	1996 / England	14	14	0	1
Ortiz *et al*	1996 / Spain	93	95	0	0
Hartsell *et al*	1997 / USA	29	29	0	1
Nessim *et al*	1997 / USA	27	27	0	0
Stewart *et al*	1998 / Australia	40	40	0	1
Hans-Geurts *et al*	2001 / The Netherlands	56	49	0	3
Delaney *et al*	2003 / USA	31	33	0	0
Lucha *et al*	2005 / USA	26	25	0	0
Zhou *et al*	2006 / China	161	155	0	0
Hans-Geurts *et al*	2007 / The Netherlands	46	50	3	1

Table C.4 - Complications

Author	Year / Country	n =		Total complications		
		early	control	early	control	**excluding nausea and vomiting**
Sagar *et al*	1979 / England	15	15	3	5	
Ryan *et al*	1981 / USA	7	7	2	7	appears to only include IVF related complications
Schroeder *et al*	1991 / New Zealand	16	16	4	7	
Binderow *et al*	1993 / USA	32	32	0	0	
Beier-Holgersen *et al*	1996 / Denmark	30	30	8	19	2/14 infectious complications
Carr *et al*	1996 / England	14	14	0	4	includes bleeding duodenal ulcer
Ortiz *et al*	1996 / Spain	93	95	17	18	
Hartsell *et al*	1997 / USA	29	29	1	1	
Nessim *et al*	1997 / USA	27	27	3	4	
Stewart *et al*	1998 / Australia	40	40	10	12	
Hans-Geurts *et al*	2001 / The Netherlands	56	49	12	13	
Delaney *et al*	2003 / USA	31	33	7	10	
Lucha *et al*	2005 / USA	26	25	1	1	
Zhou *et al*	2006 / China	161	155	23	70	21 vs 66 from table vs data in the text; multiple requests for clarification not responsed to
Hans-Geurts *et al*	2007 / The Netherlands	46	50	22	20	includes ileus, excludes mortality

discrepancy within figures reported

Table C.5 - Anastomotic Dehiscence

Author	Year / Country	n =		Anastomotic Dehiscence	
		early	control	early	control
Sagar *et al*	1979 / England	15	15	0	1
Ryan *et al*	1981 / USA	7	7	n/a	n/a
Schroeder *et al*	1991 / New Zealand	16	16	0	0
Binderow *et al*	1993 / USA	32	32	n/a	n/a
Beier-Holgersen *et al*	1996 / Denmark	30	30	2	4
Carr *et al*	1996 / England	14	14	0	0
Ortiz *et al*	1996 / Spain	93	95	2	4
Hartsell *et al*	1997 / USA	29	29	0	1
Nessim *et al*	1997 / USA	27	27	0	0
Stewart *et al*	1998 / Australia	40	40	1	0
Hans-Geurts *et al*	2001 / The Netherlands	18	19	2	1
Delaney *et al*	2003 / USA	31	33	0	0
Lucha *et al*	2005 / USA	26	25	1	0
Zhou *et al*	2006 / China	161	155	2	4
Hans-Geurts *et al*	2007 / The Netherlands	42	35	2	2

n=from paper for pts with anastomoses

n/a = not available

Table C.6 – Days to Passage of Flatus

Author	Year / Country	n =		Days to passing flatus		Notes
		early	control	early	control	
Sagar *et al*	1979 / England	15	15	n/a	n/a	
Ryan *et al*	1981 / USA	7	7	n/a	n/a	
Schroeder *et al*	1991 / New Zealand	16	16	2.41±1.33	2.91±1.29	reported in hours, converted to days -
Binderow *et al*	1993 / USA	32	32	3.6	4	**return of bowel activity= either PF or BM Pg 585**
Beier-Holgersen *et al*	1996 / Denmark	30	30	2	3	
Carr *et al*	1996 / England	14	14	6	6	
Ortiz *et al*	1996 / Spain	93	95	n/a	n/a	
Hartsell *et al*	1997 / USA	29	29	n/a	n/a	
Nessim *et al*	1997 / USA	27	27	n/a	n/a	
Stewart *et al*	1998 / Australia	40	40	3 (1-5)	4 (2-6)	
Hans-Geurts *et al*	2001 / The Netherlands	56	49			figures not stated in text - e-mail request 17.12.07; letter sent returned to sender
Delaney *et al*	2003 / USA	31	33	n/a	n/a	
Lucha *et al*	2005 / USA	26	25	n/a	n/a	
Zhou *et al*	2006 / China	161	155	3.0±0.9	3.6±1.2	
Hans-Geurts *et al*	2007 / The Netherlands	43	49	1 (1-7)	1 (1-4)	NB 2 missing data omitted in control group, 3 from intervention
				1.7±0.2	1.4 ±0.1	

median (range)
mean (range)
unsure of whether mean/median

Table C.7 – Days to Passage of Bowel Motion

Author	Year / Country	n =		Days to first BM		
		early	control	early	control	
Sagar *et al*	1979 / England	15	15	n/a	n/a	
Ryan *et al*	1981 / USA	7	7	4.5	5.7	**Most likely mean data as they have used mean value everywhere else - it is not clear**
Schroeder *et al*	1991 / New Zealand	16	16	3.21±1.5	4.16±1.33	reported in hours, converted to days - **OK**
Binderow *et al*	1993 / USA	32	32	3.6	4	**return of bowel activity= either PF or BM Pg 585**
Beier-Holgersen *et al*	1996 / Denmark	30	30	2.5	4	
Carr *et al*	1996 / England	14	14	4	5	
Ortiz *et al*	1996 / Spain	93	95	4.3	4.7	**Most likely mean data as they have used mean value everywhere else - it is not clear**
Hartsell *et al*	1997 / USA	29	29	n/a	n/a	
Nessim *et al*	1997 / USA	27	27	2.8	3.9	
Stewart *et al*	1998 / Australia	40	40	4 (2-9)	5 (2-8)	
Hans-Geurts *et al*	2001 / The Netherlands	56	49	1	1	
Delaney *et al*	2003 / USA	31	33	n/a	n/a	
Lucha *et al*	2005 / USA	26	25	n/a	n/a	
Zhou *et al*	2006 / China	161	155	4.1±1.1	4.8±1.4	
Hans-Geurts *et al*	2007 / The Netherlands	43	49	4 (1-9)	3 (1-10)	NB 2 missing data omitted in control group, 3 from intervention group
				4.3±0.3	3.7±0.3	

median (range)
mean (range)
unsure if mean/median

Table C.8 - Nausea and Vomiting

Author	Year / Country	n =		nausea and/or vomiting (n)		
		early	control	early	control	
Sagar *et al*	1979 / England	15	15	n/a	n/a	
Ryan *et al*	1981 / USA	7	7	n/a	n/a	
Schroeder *et al*	1991 / New Zealand	16	16	n/a	n/a	
Binderow *et al*	1993 / USA	32	32	14	8	vomiting only
Beier-Holgersen *et al*	1996 / Denmark	30	30	19	22	largest number of n/v taken to avoid combing
Carr *et al*	1996 / England	14	14	1	7	nausea or vomiting
Ortiz *et al*	1996 / Spain	93	95	13	8	D4 data provided through correspondance with authors; vomiting only
Hartsell *et al*	1997 / USA	29	29	16	15	numbers not provided - extrapolated from % given; largest % of N&V taken
Nessim *et al*	1997 / USA	27	27	3	7	didn't differentiate between N&V in reported figures
Stewart *et al*	1998 / Australia	40	40	14	14	vomiting only
Hans-Geurts *et al*	2001 / The Netherlands	56	49			figures not stated in text - e-mail request 17.12.07, no response
Delaney *et al*	2003 / USA	31	33	n/a	n/a	
Lucha *et al*	2005 / USA	26	25	n/a	n/a	
Zhou *et al*	2006 / China	161	155	n/a	n/a	
Hans-Geurts *et al*	2007 / The Netherlands	46	50	n/a	n/a	

Table C.9 – Number of Patients Requiring Nasogastric Tube Reinsertion

Author	Year / Country	n =		NG reinsertion (n)		
		early	control	early	control	
Sagar *et al*	1979 / England	15	15	n/a	n/a	
Ryan *et al*	1981 / USA	7	7	n/a	n/a	
Schroeder *et al*	1991 / New Zealand	16	16	n/a	n/a	
Binderow *et al*	1993 / USA	32	32	6	4	
Beier-Holgersen *et al*	1996 / Denmark	30	30	n/a	n/a	
Carr *et al*	1996 / England	14	14	n/a	n/a	
Ortiz *et al*	1996 / Spain	93	95	20	not stated	
Nessim *et al*	1997 / USA	29	29	n/a	n/a	
Hartsell *et al*	1997 / USA	27	27	7.83	4.64	
Stewart *et al*	1998 / Australia	92	103	4	3	
Hans-Geurts *et al*	2001 / The Netherlands	56	49	9	9	
Delaney *et al*	2003 / USA	31	33	2	3	
Lucha *et al*	2005 / USA	26	25	5	3	
Zhou *et al*	2006 / China	161	155	3	1	data extrapolated from texts
Hans-Geurts *et al*	2007 / The Netherlands	46	50	11	5	

Table C.10 - Length of Hospital Stay

Author	**Year / Country**	**n =**		**LOS in days**		
		early	**control**	**early**	**control**	
Sagar *et al*	1979 / England	15	15	14 (10-26)	19 (10-46)	
Ryan *et al*	1981 / USA	7	7	n/a	n/a	
Schroeder *et al*	1991 / New Zealand	16	16	10±4	15±10	
Binderow *et al*	1993 / USA	32	32	6.7 (3-16)	8 (3-18)	
Beier-Holgersen *et al*	1996 / Denmark	30	30	8	11.5	
Carr *et al*	1996 / England	14	14	9.8±6.6	9.3±2.8	
Ortiz *et al*	1996 / Spain	93	95	n/a	n/a	
Hartsell *et al*	1997 / USA	29	29	7.2±3.3	8.1±2.3	
Nessim *et al*	1997 / USA	27	27	3.7	4.4	
Stewart *et al*	1998 / Australia	40	40	9 (5-28)	11 (6-18)	
Hans-Geurts *et al*	2001 / The Netherlands	56	49	11 (3-72)	11 (6-34)	
Delaney *et al*	2003 / USA	31	33	5.2±2.5	5.8±3	primary length of stay
Lucha *et al*	2005 / USA	26	25	6.3	6.6	**Most like mean or average values**
Zhou *et al*	2006 / China	161	155	8.4±3.4	9.6±5.0	
Hans-Geurts *et al*	2007 / The Netherlands	46	49	9 (4-81)	8 (5-160)	NB 2 missing datas in control group
				12±1.8	17.5±4.2	

median (range) or ±SD

mean (range) or ±SD

unsure of whether mean/median -- ? Presence of ± indicates mean by association of SEM???

Appendix D – Funnel Plots

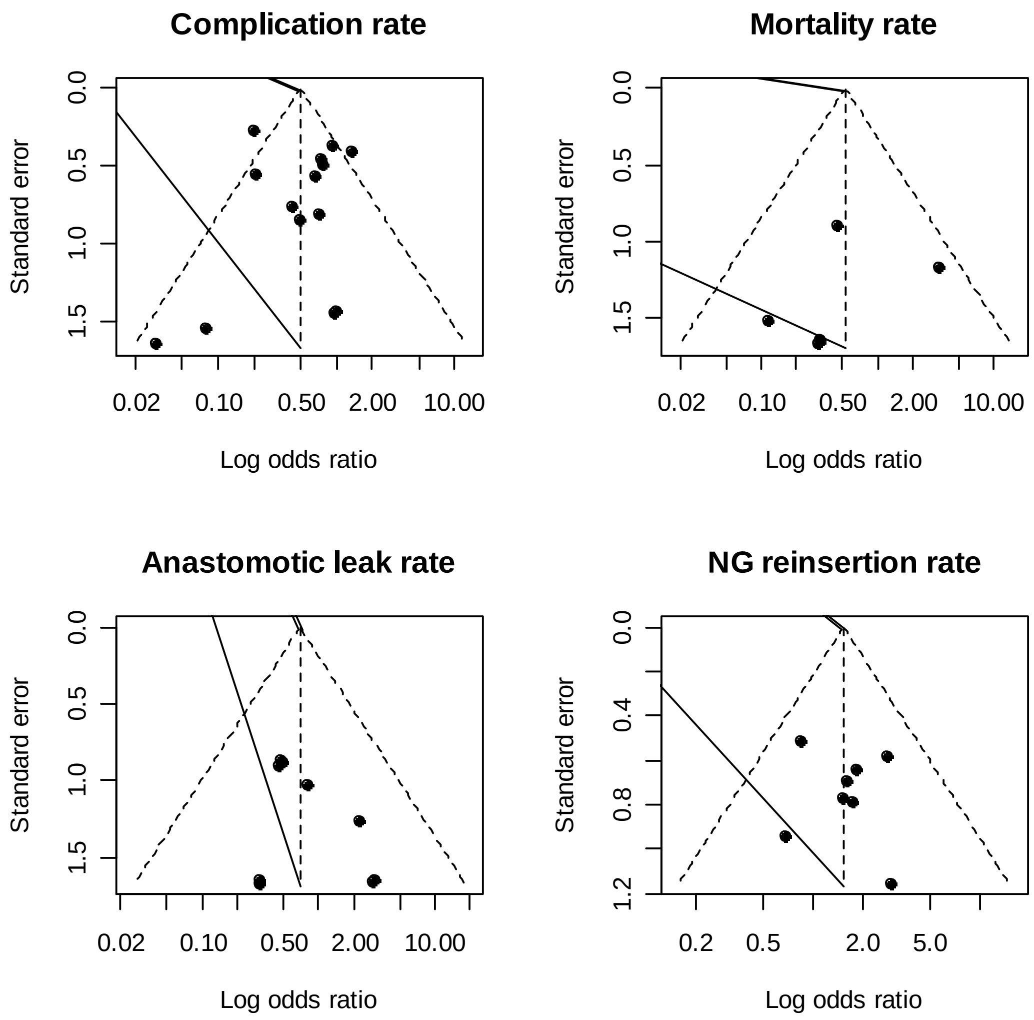

Figure D.1 – Funnel Plots Log OR vs Standard Error (Binary Outcomes). The variables reported are complications, mortality, anastomotic dehiscence, and nasogastric reinsertion as included in the early versus traditional feeding trials. The points correspond to the treatment effects (log OR) of the studies that report on the reported variable, and the diagonal lines show the expected 95% confidence intervals around the pooled fixed effect log odds ratio estimate

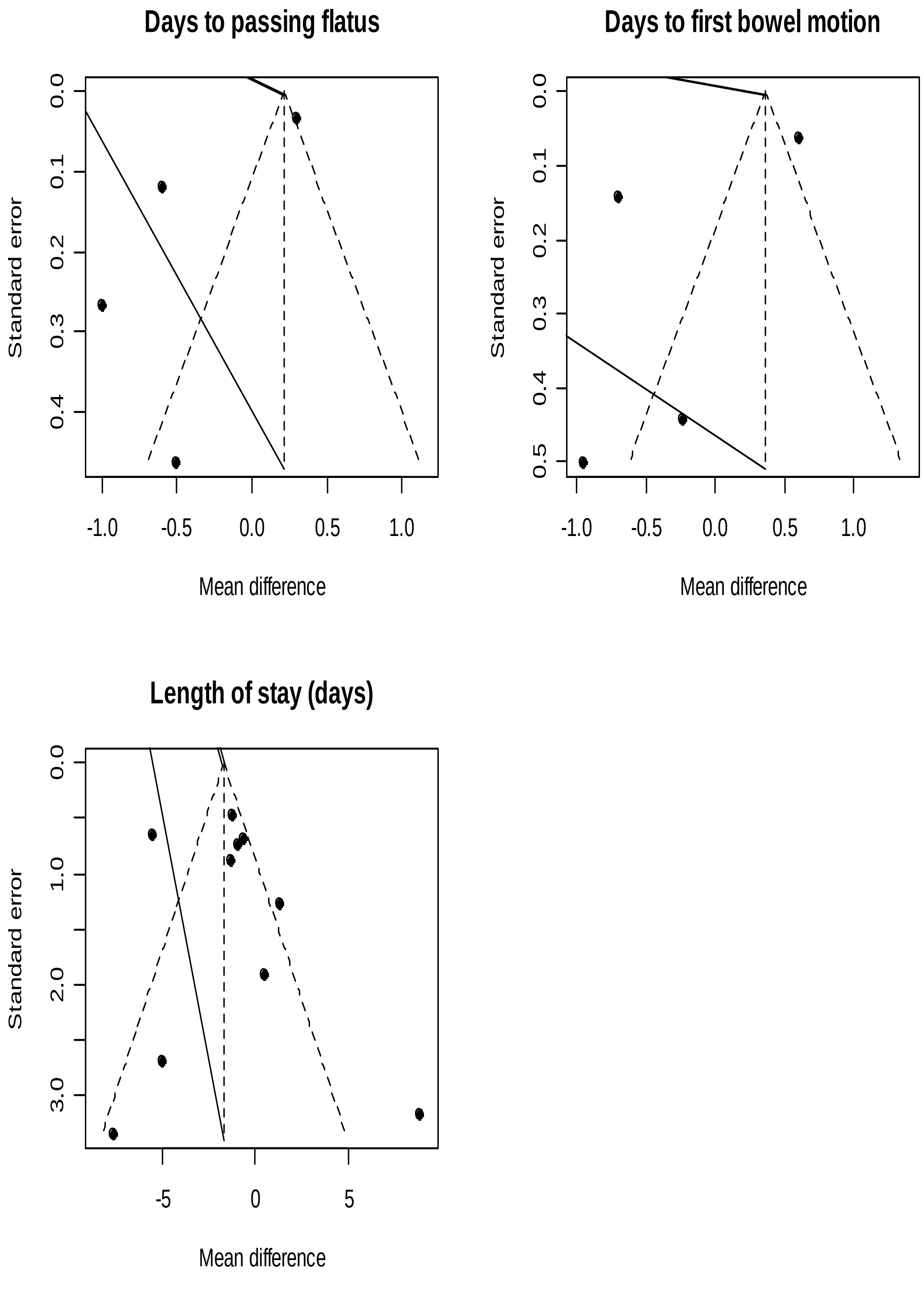

Figure D.2 – Funnel Plots Log OR vs Standard Error (Continuous Outcomes). The variables reported variables are days to passage of flatus, days to first bowel motion and length of hospital stay as reported in the included early versus traditional feeding trials. The points correspond to the treatment effects (mean difference) of the studies that report on the reported variable, and the diagonal lines show the expected 95% confidence intervals around the pooled fixed effect log odds ratio estimate.

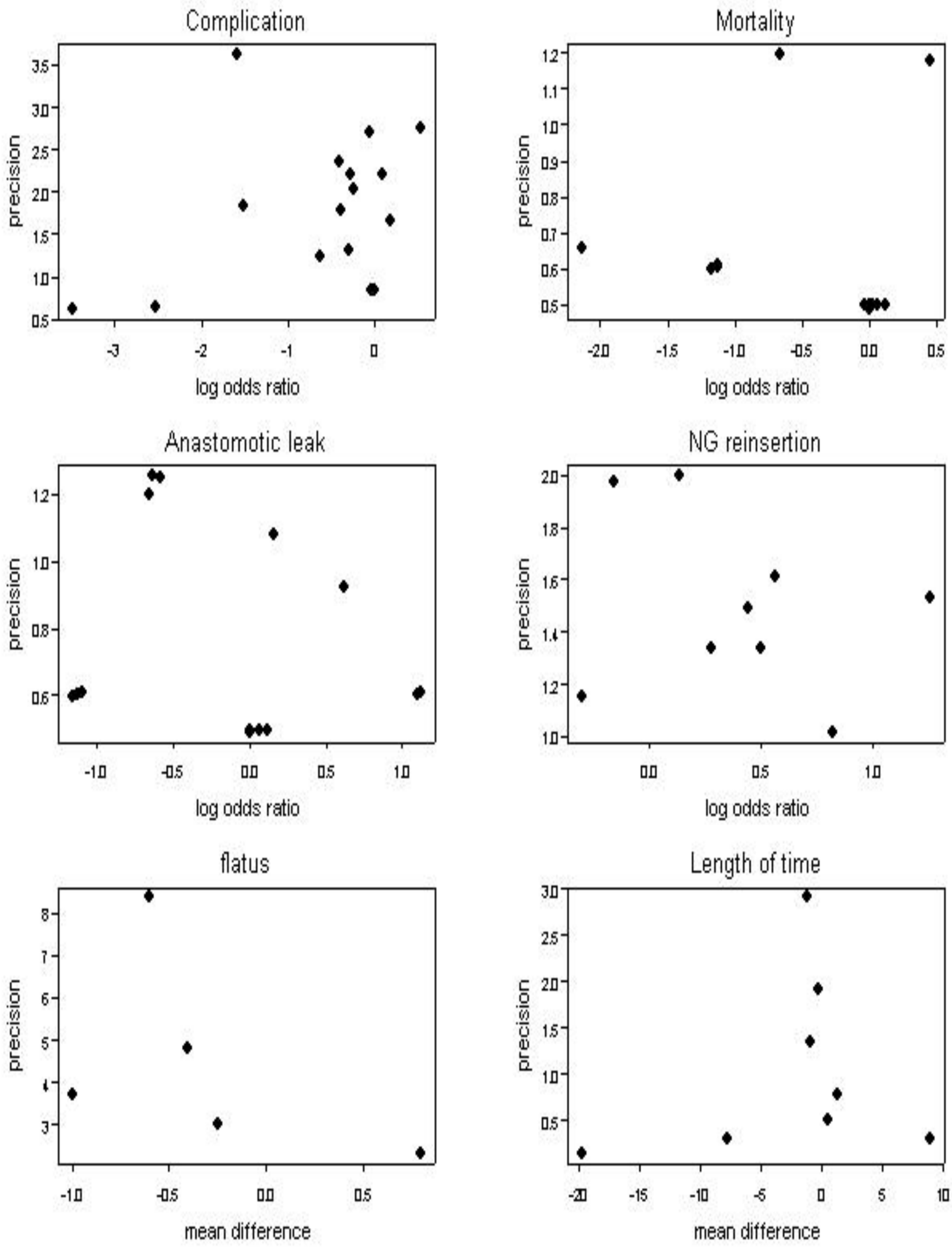

Figure D.3 – Funnel Plots Log OR vs Precision (1/standard error) for complications, mortality, anastomotic dehiscence, nasogastric reinsertion, days to passage of flatus and length of hospital stay in the included early versus traditional feeding trials. The points correspond to the treatment effects (log OR for binary or mean difference for continuous outcomes respectively) of the studies that report on the reported variable.

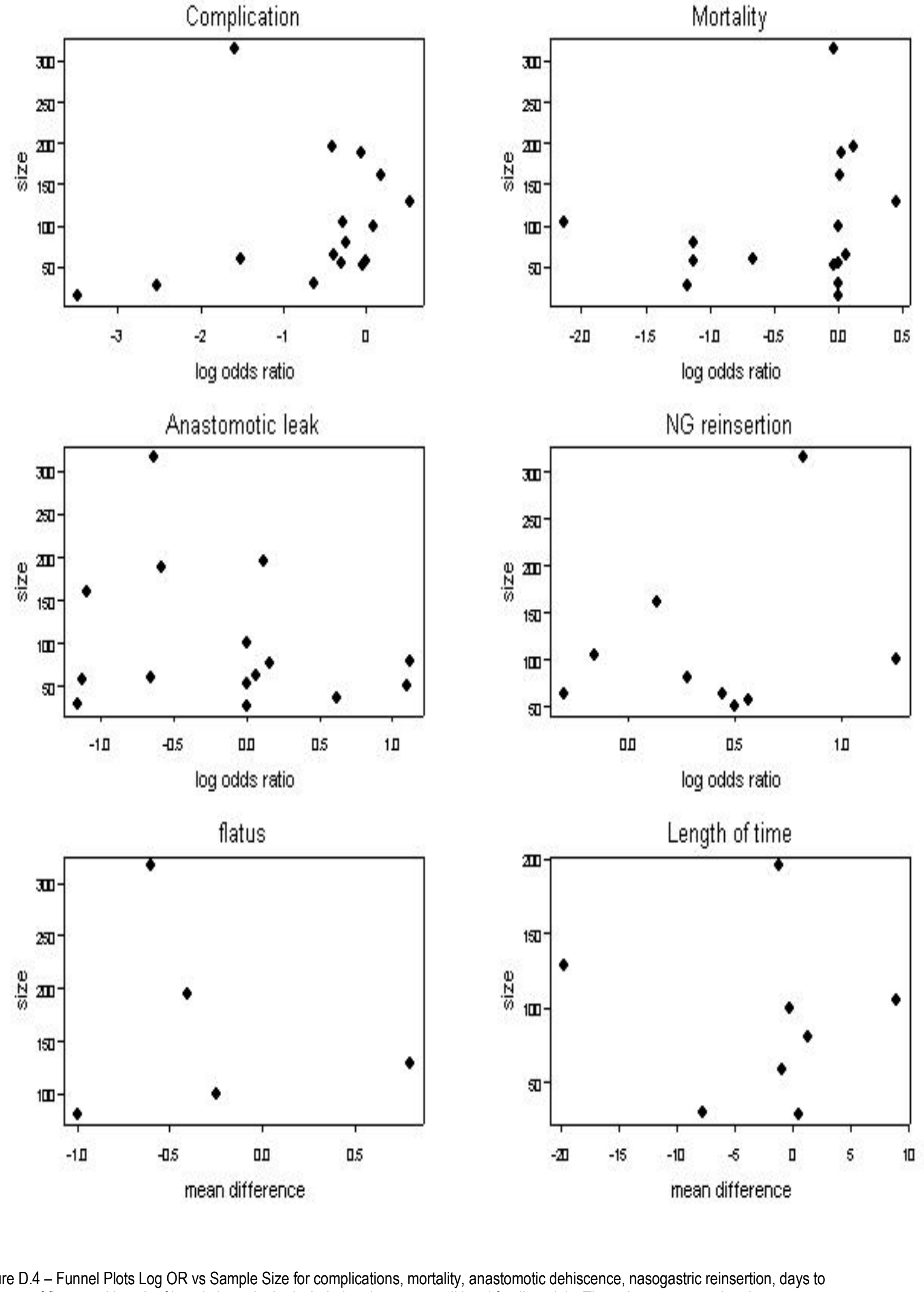

Figure D.4 – Funnel Plots Log OR vs Sample Size for complications, mortality, anastomotic dehiscence, nasogastric reinsertion, days to passage of flatus and length of hospital stay in the included early versus traditional feeding trials. The points correspond to the treatment effects (log OR for binary or mean difference for continuous outcomes respectively) of the studies that report on the reported variable.

Appendix E – Analysis of Binary Outcomes Using Relative Risk Ratios

Table E.1 Outcomes of Binary Outcomes using Relative Risk Ratios

Outcomes Variables	**Year published**	**Number of studies**	**Number of patients evaluated**	**Pooled RR**	**Test for overall effect**		**Test for heterogeneity**		
					Z	p	χ^2	p	I-squared index
Complications (nausea and vomiting excluded)	Pre 2000	10	608	0.65 (0.48,0.87)	-2.89	0.0038	5.20	0.8169	0%
	Post 2000	5	632	0.69 (0.41,1.17)	-1.37	0.1700	12.55	0.0137	68%
	1970 – 2007	**15**	**1240**	**0.65 (0.51,0.83)**	**-3.50**	**0.0005**	**17.98**	**0.2077**	**22%**
Mortality	Pre Post	10	605	0.60 (0.24,1.50)	-1.10	0.2729	0.79	0.9998	0%
	Post 2000	5	632	1.04 (0.29,3.79)	0.06	0.9514	2.78	0.5951	0%
	1970 – 2007	15	1240	0.72 (0.34,1.53)	-0.86	0.3915	4.00	0.9955	0%
Anastomotic dehisence	Pre 2000	8	530	0.64 (0.27, 1.48)	-1.05	0.2945	1.41	0.9852	0%
	Post 2000	5	545	0.95 (0.38,2.35)	-0.12	0.9057	1.36	0.8517	0%
	1970 – 2007	13	1075	0.77 (0.41,1.42)	-0.85	0.3961	3.10	0.9948	0%
NG reinsertion	Pre 2000	3	313	1.49 (0.79,2.8)	1.24	0.2168	0.01	0.9954	0%
	Post 2000	5	632	1.32 (0.8,2.18)	1.10	0.2713	2.60	0.6262	0%
	1970 – 2007	8	945	1.38 (0.94,2.05)	1.63	0.1033	2.67	0.9139	0%

RR = Relative Risk Ratio

Study	Early	Traditional	RR	L	U
pre 2000					
Sagar	3 of 15	5 of 15	0.64	0.19	2.14
Ryan	2 of 7	7 of 7	0.33	0.11	1
Schroeder	4 of 16	7 of 16	0.6	0.21	1.69
Binderow	0 of 32	0 of 32	1	0.02	50
Beier-Holgersen	8 of 30	19 of 30	0.44	0.2	0.93
Carr	0 of 14	4 of 14	0.11	0.01	1.94
Ortiz	17 of 93	18 of 95	0.97	0.47	1.99
Hartsell	1 of 29	1 of 29	1	0.11	9.43
Nessim	3 of 27	4 of 27	0.78	0.2	3.03
Stewart	10 of 40	12 of 40	0.84	0.37	1.89
subtotal	**48 of 303**	**77 of 305**	**0.65**	**0.48**	**0.87**
post 2000					
Hans-Geurts	12 of 56	13 of 49	0.81	0.37	1.78
Delaney	7 of 31	10 of 33	0.76	0.31	1.87
Lucha	1 of 26	1 of 25	0.96	0.1	9.01
Zhou	23 of 161	70 of 155	0.32	0.18	0.58
Hans-Geurts	22 of 46	20 of 50	1.19	0.65	2.2
subtotal	**65 of 320**	**114 of 312**	**0.69**	**0.41**	**1.17**
POOLED	**113 of 623**	**191 of 617**	**0.65**	**0.51**	**0.83**

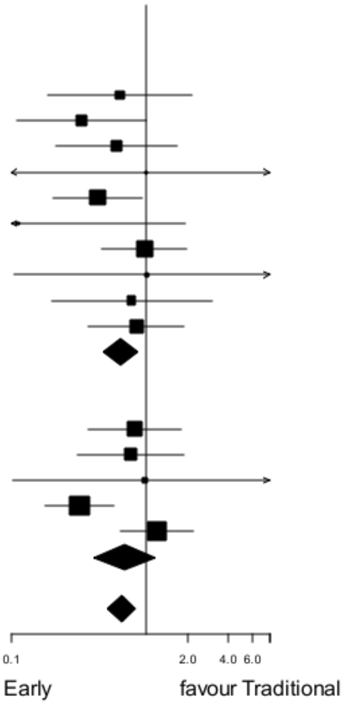

Figure E.1 – Forest Plot for Relative Risk Ratios of Postoperative Complications. Values in left panel are observed counts for Early and Traditional feeding, relative risk and limits of 95% confidence intervals for relative risk of the outcome variable. In the graph, squares indicate point estimates of treatment effect (relative risk for Early over Traditional groups) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for relative risk of individual studies. The pooled estimate for the complication rate is the pooled relative risk, obtained by combining all relative risk of the 15 studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at one favour early feeding.

Study	Early	Traditional	RR	L	U
pre 2000					
Sagar	0 of 15	0 of 15	1	0.02	47.29
Ryan	0 of 7	0 of 7	1	0.02	44.13
Schroeder	0 of 16	0 of 16	1	0.02	47.47
Binderow	0 of 32	0 of 32	1	0.02	48.9
Beier-Holgersen	2 of 30	4 of 30	0.56	0.13	2.4
Carr	0 of 14	1 of 14	0.33	0.01	7.52
Ortiz	0 of 93	0 of 95	1.02	0.02	50.95
Hartsell	0 of 29	1 of 29	0.33	0.01	7.85
Nessim	0 of 27	0 of 27	1	0.02	48.63
Stewart	0 of 40	1 of 40	0.33	0.01	7.94
subtotal	**2 of 303**	**7 of 305**	**0.6**	**0.24**	**1.5**
post 2000					
Hans-Geurts	0 of 56	3 of 49	0.13	0.01	2.36
Delaney	0 of 31	0 of 33	1.06	0.02	52
Lucha	0 of 26	0 of 25	0.96	0.02	46.7
Zhou	0 of 161	0 of 155	0.96	0.02	48.23
Hans-Geurts	3 of 46	1 of 50	2.53	0.39	16.46
subtotal	**3 of 320**	**4 of 312**	**1.04**	**0.29**	**3.79**
POOLED	**5 of 623**	**11 of 617**	**0.72**	**0.34**	**1.53**

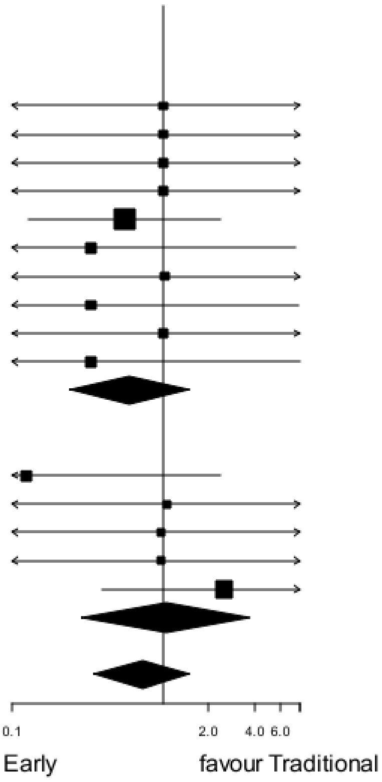

Figure E.2- Forest Plot for Relative Risk Ratios of Mortality. Values in left panel are observed counts for Early and Traditional feeding, relative risk and limits of 95% confidence intervals for relative risk of the outcome variable. In the graph, squares indicate point estimates of treatment effect (relative risk for Early over Traditional groups) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for relative risk of individual studies. The pooled estimate for the mortality rate is the pooled relative risk, obtained by combining all relative risk of the 13 studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at one favour early feeding.

Study	Early	Traditional	RR	L	U
pre 2000					
Sagar	0 of 15	1 of 15	0.33	0.01	7.57
Schroeder	0 of 16	0 of 16	1	0.02	47.47
Beier-Holgersen	2 of 30	4 of 30	0.56	0.13	2.4
Carr	0 of 14	0 of 14	1	0.02	47.08
Ortiz	2 of 93	4 of 95	0.57	0.12	2.59
Hartsell	0 of 29	1 of 29	0.33	0.01	7.85
Nessim	0 of 27	0 of 27	1	0.02	48.63
Stewart	1 of 40	0 of 40	3	0.13	71.49
subtotal	**5 of 264**	**10 of 266**	**0.64**	**0.27**	**1.48**
post 2000					
Hans-Geurts	2 of 18	1 of 19	1.76	0.26	12
Delaney	0 of 31	0 of 33	1.06	0.02	52
Lucha	1 of 26	0 of 25	2.89	0.12	67.65
Zhou	2 of 161	4 of 155	0.53	0.12	2.47
Hans-Geurts	2 of 42	2 of 35	0.84	0.15	4.55
subtotal	**7 of 278**	**7 of 267**	**0.95**	**0.38**	**2.35**
POOLED	**12 of 542**	**17 of 533**	**0.77**	**0.41**	**1.42**

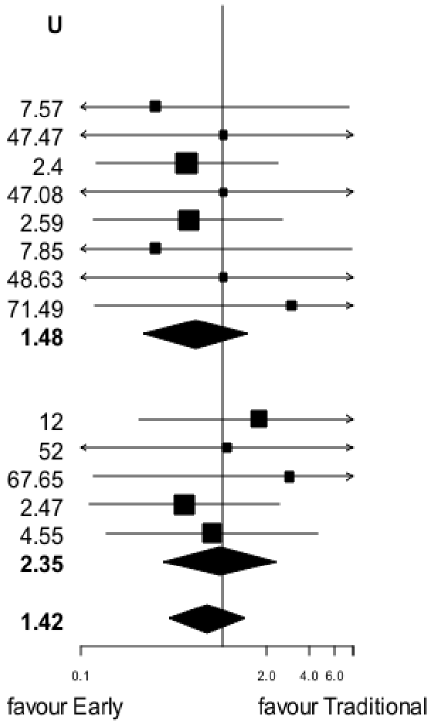

Figure E.3 – Forest Plot for Relative Risk Ratios of Anastomotic Dehiscence. Values in left panel are observed counts for Early and Traditional feeding, relative risk and limits of 95% confidence intervals for relative risk of the outcome variable. In the graph, squares indicate point estimates of treatment effect (relative risk for Early over Traditional groups) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for relative risk of individual studies. The pooled estimate for the anastomotic dehisence rate is the pooled relative risk, obtained by combining all relative risk of the 13 studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at one favour early feeding.

Study	Early	Traditional	RR	L	U
pre 2000					
Binderow	6 of 32	4 of 32	1.44	0.48	4.34
Hartsell	8 of 27	5 of 27	1.55	0.61	3.93
Stewart	4 of 92	3 of 103	1.44	0.37	5.65
subtotal	**18 of 151**	**12 of 162**	**1.49**	**0.79**	**2.8**
post 2000					
Hans-Geurts	9 of 56	9 of 49	0.88	0.39	1.98
Delaney	2 of 31	3 of 33	0.76	0.16	3.57
Lucha	5 of 26	3 of 25	1.51	0.44	5.15
Zhou	3 of 161	1 of 155	2.25	0.34	15.02
Hans-Geurts	12 of 61	7 of 67	2.27	0.89	5.78
subtotal	**30 of 320**	**21 of 312**	**1.32**	**0.8**	**2.18**
POOLED	**48 of 471**	**33 of 474**	**1.38**	**0.94**	**2.05**

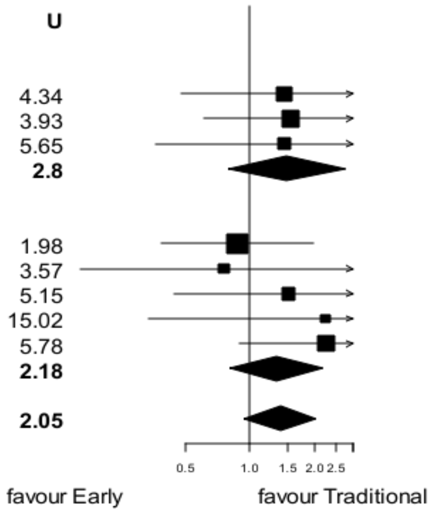

Figure E.4 – Forest Plot for Relative Risk Ratios of Nasogastric Tube Reinsertion. Values in left panel are observed counts for Early and Traditional feeding, relative risk and limits of 95% confidence intervals for relative risk of the outcome variable. In the graph, squares indicate point estimates of treatment effect (relative risk for Early over Traditional groups) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for relative risk of individual studies. The pooled estimate for the NG reinsertion rate is the pooled relative risk, obtained by combining all relative risk of the 8 studies using the inverse variance weighted method. The 95% confidence interval for the pooled estimate is represented by the diamond and the length of the diamond depicts the width of the confidence interval. Values to the left of the vertical line at one favour early feeding.

Appendix F – Glossary of Terms

(med) = medical or surgical terminology
(nutr) = nutritional terminology
(stat) = statistical terminology
(res) = research terminology

A Priori analysis – (stat) An analysis planned in advance; stated in the study's methodology (Green and Higgins, 2005).

Abdominoperitineal resection – (med) Pertaining to the surgical removal of part of the abdomen and peritoneum.

Acute Phase Response – (med) The metabolic response to injury or infection in which a cascade of inflammatory reactions occurs within the body mediated by cellular messengers such as cytokines (Sobotka et al., 2004).

Adipose – (med) Pertaining to fat cells; adipose tissue relates to the fatty tissues of the body.

Afferent – (med) A term used for nerves, blood vessels and lymphatics that move towards the centre. For example, an afferent nerve refers to one that moves the periphery to the spinal cord.

Albumin – (med) A type of protein present in the blood. Traditionally used as nutritional indicator though it is ill suited to this use due to its role as a negative acute phase protein (serum concentrations reduced in times of metabolic stress such as following surgery or during sepsis or infection).

Anabolic – (med) Metabolic processes in which simple substances are converted into more complex forms. This includes formation of proteins from amino acids, and storage of fat in adipose tissue from circulating fatty acids or glucose.

Anaerobic – (med) Pertaining to the absence of oxygen or air. Anaerobic metabolism is that that does not requiring oxygen to function.

Anastomosis – (med) Internal surgical site; the point where two anatomical structures have been joined by the surgeon, i.e. the surgical join between two parts of bowel where a segment between them has been removed.

Anastomotic – (med) Pertaining to an anastomosis.

Anthropometric – (nutr) adjective of **Anthropometry**, "The science of measuring the human body as to height, weight and size of component parts including skinfolds, to study and compare the relative proportions under normal and abnormal conditions" (p. 100).

Atelectasis – (med) Collapse of the alveoli of the lung resulting in reduced oxygen and carbon dioxide exchange; may result in respiratory complications such as pneumonia; may be caused by anaesthesia during surgery.

Bacterial translocation – (med) Movement of bacteria from the lumen of the intestines into the bloodstream and potentially to distant organs. This is thought to occur in times when the integrity of the brush border of the small intestine is disrupted such as during prolonged fasting or metabolic stress (Winkler and Malone, 2008).

Binary - (stat) An outcome or variable in which only one of two categorical outcomes is possible. Examples include death, development of complication/s or heart attack (Higgins and Green, 2006).

Catabolism – (med) Process whereby body tissues are broken down to liberate substrate and energy required to meet metabolic requirements. For example, adipose tissue broken down to generate energy, or muscles broken down to make amino acids available for gluconeogenesis (Champe and Harvey, 1994).

Catecholamine – (med) A class of hormones produced by the adrenal gland in response to shock. Examples include adrenalin and dopamine (Winkler and Malone, 2008).

Clear fluids – (nutr) A commonly used medical diet characterised by the provision of fluids that are transparent and liquid at room temperature. Examples include broth, apple juice, flat lemonade or gingerale and jelly. This diet is deficient in many essential nutrients including protein, fat, vitamins and minerals (Hancock, Cresci and Martindale, 2002).

Colectomy – (med) Surgical removal of part or all of the large bowel.

Continuous – (stat) An outcome or variable that is measured in numerical quantities in which smaller fractions of the measured unit can be obtained. Common examples include weight, height and days (Higgins and Green, 2006).

Correlation co-efficient – (stat) Measure of linear association between two variables. A correlation co-efficient can range from -1 (perfect correlation in a downward direction) to +1 (perfect correlation in an upward direction), and 0 reflects no correlation (Green and Higgins, 2005). Denoted by r (De Veaux, Velleman and Bock, 2006).

Cortisol – (med) A counter-regulatory steroid hormone produced in the adrenal gland (Winkler and Malone, 2008).

Counter-regulatory hormones – (med) Hormones produced in response to physiological stress such as trauma or a reduction in blood sugar levels, and function to release stored glucose and fatty acids from body stores, that is they, they induce catabolism. Examples of counter-regulatory hormones include glucagon, adrenaline, noradrenaline, cortisol and growth hormone (Franz, 2008).

C-Reactive Protein – (med) A protein found in the blood when inflammation or necrosis is present, and absent when no inflammation is present or if the inflammatory processes are suppressed with medications.

Cytokines – (med) Proinflammatory proteins involved in cell to cell communication, co-ordination of antibody and T cell immune interactions and the amplification of immune reactions. Examples of cytokines include interferon, interleukin-1, and tumour necrosis factor (Winkler and Malone, 2008).

Dehiscence – (med) Breakdown or rupture of a surgical wound.

Dispersion – (stat) A blanket term for the variability or spread within a data set. Measure of dispersion include range, standard deviation and interquartile range (Wikipedia, 2009b).

Distal – (med) Further from the point of origin or reference. Distal feeding refers to nutrition being introduced past the surgical site, that is, to totally bypass the anastomosis.

Efferent – (med) A term used for nerves, blood vessels and lymphatics that move away from the centre. For example, an efferent nerve refers to one that moves from the spinal cord to the periphery.

Elemental nutritional formula – (nutr) A form of nutrition in which the protein sources are provided as amino acids, i.e. Vivonex TEN® (Nestle Healthcare Nutrition, Minneapolis, USA). It is designed for ease of absorption as no digestion is required (Sobotka et al., 2004).

Emesis – (med) Vomiting.

Endogenous – (med) Derived internally from the body. For example, hydrochloric acid secretions from the stomach or insulin from the pancreas.

Enteral – (med) Relates to the intestinal tract. Enteral feeding relates providing nutrition directly into the stomach or small bowel via a feeding tube.

Enteric – (med) Relates to the intestinal tract.

Epidural analgesia – (med) Pain relieving and anaesthetic technique in which local anaesthetic is injected into the epidural space around the dural membrane to allow a loss of or reduced sensation below the point of entry. A type of regional neuraxial blockade.

Epidural space – (med) The area above or outside of the outermost membrane of the brain and spinal cord.

Febrile – (med) Raised temperature, generally considered to be over 37.8°C; a fever; generally indicative of an infection.

Fibroblasts – (med) "Undifferentiated cell in the connective tissue that gives rise to ... cells that tissues for the body" (p. 630).

Fistula – (med) "An abnormal passage from an internal organ to the body surface or between two internal organs" (pp. 637-8).

Fixed effect model – (stat) A model of meta-analysis in which combined estimates are calculated based on the assumption that there is only one true effect size in the included studies, and as such the only within variation is present. Weights are assigned using inverse variance of the within-study variation (Borenstein, Hedges and Rothstein, 2007).

Flatus – (med) Intestinal gas passed from the rectum.

Free Fluids – (nutr) A commonly used medical diet characterised by the provision of fluids that include dairy foods and porridge as well as the contents of a clear fluid diet. Nutritional adequacy is possible on this diet, particularly with the use of commercial liquid nutritional supplements (Sobotka et al., 2004).

Funnel plot – (stat) A form of scatter plot traditionally used for the detection of publication bias in meta-analyses. In the absence of publication bias the shape of an inverted funnel should be evident when the variable is plotted against the standard error (Higgins and Green, 2006).

Gastric Decompression – (med) Removal of pressure caused by gas or liquid from the stomach, usually with a nasogastric tube.

General Anaesthesia – (med) Loss of sensation and consciousness induced by the inhalation or intravenous injection of one or more anaesthetic drugs. By way of comparison general anaesthesia 'puts to sleep' the whole body while regional anaesthesia only the affects the desired part/s.

Glucagon – (med) Hormone produced in the pancreas in times of low blood sugar or in response to Growth Hormone that stimulates the conversion of glycogen (stored glucose) to glucose in the liver.

Gluconeogensis – (med) Metabolic process whereby glucose is produced from triglycerides or amino acids (Champe and Harvey, 1994).

Glutathione – (med) Protein made up of the amino acids glutamic acid, cysteine and glycine that has antioxidant function.

Glycolysis – (med) breakdown of glucose to release energy for metabolism; can be aerobic (glucose broken down to pyruvic acid) or anaerobic (glucose broken down to lactic acid) process.

Gortex – Plastic polymer composed of polytetrafluoroethylene; porous in nature and with microstructure of nodes and interconnected fibrils, produced by WL Gore and Associates, Flagstaff, AZ, USA. In the Schroeder et al study tubing made of this substance was implanted into patient's forearms and the amount of hydroxyproline removed from the porous structure was used as an indication of wound healing capability (Schroeder et al., 1991; Wikipedia, 2009a).

Gut-Associated Lymphoid Tissue [GALT] – (med) Lymphatic tissue located within the intestinal mucosal layer of the gut that provides immune protection to the body, and may protection against multiple organ dysfunction (Winkler and Malone, 2008).

Heterogeneity – (stat) Dissimilar in nature or quality. Statistical tests of heterogeneity in a meta-analysis such as the Q test or I^2 Index test for the presence of differences within the dataset being analysed. The presence of heterogeneity may indicate a meta-analysis is inappropriate as data may not be combinable (Huedo-Medina et al., 2006).

Homogeneity – (stat) Similar in nature or quality. Homogeneity is the null hypothesis tested in statistical tests of heterogeneity such as the Q test or I^2 Index (Huedo-Medina et al., 2006).

Homeostasis – (med) The normal steady state of the body maintained by a variety of processes such as hormonal and brainstem function; The "relative constancy in the internal environment of the body maintained by natural adaptive response that promote ... survival" (pp. 770-1).

Hydroxyproline – (med) A protein composed of the amino acid proline with a hydroxyl group added. It is a component of collagen, a fibrous protein that has an important structural role in the body, including in wound healing (Champe and Harvey, 1994).

Ileus – (med) Inhibition of bowel activity, as evidenced by cessation of flatus or bowel motions (Correia and da Silva, 2004). Ileus can occur for a number of reasons, however in this context a postoperative or paralytic ileus may be considered to be a physiological response to the stress of surgery resulting in impairment of bowel motility (Correia and da Silva, 2004).

Immune-enhancing enteral feed products – (nutr) Specially formulated enteral feeding products containing pharmacological levels of nutrients, most commonly arginine and/or omega 3 fatty acids, glutamine, and ribonucleic acids, believed to confer immune enhancing benefits when compared to standard nutritional formulations. i.e. Impact® (Nestle Nutrition, Minneapolis, USA) (Sobotka et al., 2004).

Insulin – (med) A hormone produced in the pancreas that lowers blood glucose levels.

Insulin Resistance – (med) A condition in which the body's response to insulin is reduced resulting in elevated blood sugar levels. This may be associated with a number of medical conditions including diabetes mellitus and during times of physiological stress.

Ischaemic – (med) Decreased supply of oxygen to a part of the body or organ.

Jadad Score – (res) A five point score assessing randomised controlled trial study methodological quality. Points are allocated for reporting of method of randomisation, blinding, and participant withdrawal. A score of five indicates a study of highest methodologically quality, while a score of zero indicates a study of poor methodological quality (Jadad et al., 1996).

Jejunal – (med) Pertaining to the second part of the small intestine.

Jejunal feeding – (nutr) Feeding directly into the small intestine via a nasojejunal tube or jejunostomy.

Jejunostomy – (med) "Surgical procedure to create an artificial opening to the jejunum through the abdominal wall" (p. 885). In the context of the present work the procedure is undertaken to allow a route for nutritional provision directly into the small intestine.

Laryngectomy – (med) Surgical removal of the larynx.

Lipolysis – (med) breakdown of fat tissue.

Linear Regression – (stat) The investigation of two continuous variables present within each individual studied, plotted on a scatter plot, in which a line of best fit can be constructed for the variables being studied (De Veaux et al., 2006).

Location Bias – (stat) A systematic distortion of the data resulting from the method or circumstances under which the studies for a meta-analysis have been obtained. Examples of sources of location bias include inclusion of English-language only publications and exclusive use of electronic databases during literature review (Egger and Smith, 1998).

Log Odds Ratio - (stat) The odds ratio presented in its logarithmic form, abbreviated to Log OR; used to plot odds ratios on a forest plot as it allows effect sizes of equal magnitude but in opposing directions to be presented equidistant from zeros to facilitate interpretation (Galbraith, 1988).

Luminal – (med) Relating to tubular cavities within organs or within the body, for example, the large or small intestine.

Macrophages - (med) "Phagocytic cell in the reticuloendotheial system including the Kupffer's cells in the liver and spleen" (pp. 974-5).

Malignant – (med) Cancerous.

Mesenteric lymph – (med) Lymphatic tissue within the double layer of peritoneum in which the intestines are suspected from on the posterior abdominal wall.

Mini-laparotomy – (med) A modified approach to 'open' abdominal surgery in which the length of the surgical incision is minimised to under 15cm in length (Evans et al., 2008).

Nasojejunal tube – (nutr) A feeding tube placed via the nostril down the back of the throat, through the stomach and into the jejunum for provision of nutrition directly into the small intestine.

Negative Acute Phase Response Protein – (med) Produced by the liver in during times of inflammation and metabolic stress, i.e. during an acute phase response. Albumin is a negative acute phase response protein (Winkler and Malone, 2008).

Neuraxial blockade – (med) A regional anaesthetic technique in which only a selected part of the body is subjected to loss of sensation for the purpose of pain relief or anaesthesia for a surgical procedure. This is attained by injection of an anaesthetic drug into the subdural or dural space. An example of a neuraxial blockade is an epidural (Rodgers et al., 2000).

Neuroendocrine – (med) Relating to the effects produced by hormones and endocrine glands closely associated with the nervous system.

Non-malignant – (med) Not cancerous. Benign.

Non-parametric - (stat) Requiring no or only weak assumptions about the distribution of the sampled population when applied to a statistical test; used on data that are not normally distributed (Plank, 2008).

Odds – (stat) Ratio of probability that a particular event will occur to the probability that it will not occur; number can be between zero and infinity. It is most commonly expressed as an integer of two numbers. For example, 1:100 is interpreted as 1 patient in 100 or 0.01 (Higgins and Green, 2006).

Odds Ratio – (stat) Summary statistic used for binary outcomes that describes the odds of an outcome associated with an intervention. It is calculated by dividing the odds of an event in the intervention group by the odds of the event in the control group, or ad/bc where a=event occurring in the intervention group, b=event not occurring in the intervention group, c= event occurring in the control group, and d= event not occurring in the control group. Abbreviated to OR (Higgins and Green, 2006).

Oesophagogastrectomy – (med) Surgical removal of the stomach and the lower part of the oesophagus.

Overdispersion – (stat) The presence of greater variability in a set of outcomes than would be expected for a given statistical model (Wikipedia, 2008).

Parametric – (stat) Requiring strong assumptions about the distribution of the sampled population when applied to a statistical test; usually relating to the assumption of a normal distribution (Plank, 2008).

Perioperative – (med) Pertaining to the time of surgery, but also generally understood to include immediately before and immediately after an operation.

Peripheral block – (med) A regional anaesthetic technique in which only a selected part of the body is subjected to loss of sensation for the purpose of pain relief or anaesthesia for a surgical procedure. This is achieved by injection of an anaesthetic drug next to a nerve, a nerve plexus or into a compartment containing peripheral nerves (Russon, Findley and Harclerode, 2009).

Peritonitis – (med) Inflammation of the peritoneum, usually produced by bacteria or irritating substances coming in contact with the abdominal cavity following the perforation of an organ or a penetrating wound.

Pharyngolaryngitis – (med) Inflammation of the pharynx and larynx.

Polymeric – (nutr) Pertaining to whole or intact proteins. In the context of enteral feeding products it refers to formulas that contain whole proteins requiring digestion in the gastrointestinal tract prior to absorption, i.e. Jevity (Abbott Laboratories, Zwolle, The Netherlands).

Prebiotic – (nutr) Non-digestible oligosaccharides that benefit the host by selectively promoting the growth or activity of desirable bacteria in the intestinal tract; food for "good" bacteria. Examples include fructooligosaccharide and inulin (Whelan et al., 2001).

Precision – (stat) The measurement of the chance that random errors are present in the results obtained in a study, meta-analysis or measurement. It is defined as the inverse of the standard error (Green and Higgins, 2005).

Probiotic – (nutr) Live microbial component of a food, enteral feeding product or supplement that exerts a positive influence on intestinal bacteria; a "good" gut bacteria. Examples include lactobacilli, bifidobacteria and saccharomyces (Whelan et al., 2001).

Proximal – (med) Closer to the point of origin or reference. Proximal feeding refers to nutrition being introduced above the surgical site, that is, to allow nutrition to have contact with the anastomosis.

Publication Bias – (stat) Bias introduced to meta-analysis when results from unpublished studies are not included in a meta-analysis. This has the potential to pull meta-analysis results in the direction of the more commonly reported outcome/s, which may or not be reflective of the true effect (Egger and Smith, 1998).

Random effects model – (stat) A model of meta-analysis in which combined estimates are calculated based on the assumption that there are a range of true effect sizes, and as such both within and between variation is taken into account. Weights are assigned based on inverse variance but include variance from both sources (Borenstein et al., 2007).

Rank Correlation – (stat) An assessment of relationship between variables of different rankings. It is measured by a rank correlation coefficient, which measures the degree of agreement between the rankings and assesses the level of statistical significance between the agreement (Everitt, 2002).

Relative Risk – (stat) Summary statistic used for binary outcomes that describes the probability of an outcome associated with an intervention. It is calculated by dividing the risk of an event in the intervention group by the risk of the event in the control group, or [a(a+b)/c(c+d)] where a=event occurring in the intervention group, b=event not occurring in the intervention group, c= event occurring in the control group, and d= event not occurring in the control group. Abbreviated to RR (Higgins and Green, 2006).

Regional Anaesthesia – (med) Anaesthetic technique that creates a neuraxial blockade through the local injection of local anaesthetic drugs into the subarachnoid or epidural space.

This allows local efferent and afferent nerve impulses to be blocked thus alleviating pain sensations only in the area in which surgery is occurring (Rodgers et al., 2000).

Risk – (stat) Probability that an outcome will occur, usually reserved for adverse outcomes; number must fall between 0 and 1. For example, a risk of 0.2 is interpreted as 20 people out of every 100 will experience the event (Higgins and Green, 2006).

Risk Ratio – (stat) See Relative Risk.

Standard normal deviate – (stat) Defined as the odds ratio divided by its standard error. Used in the linear regression model proposed by Egger et al (1997) for the assessment of funnel plot asymmetry.

Subarachnoid space – (med) The area between the arachnoid membrane and the pia mater of the brain and spinal cord.

Subjective Global Assessment – (nutr) Considered to be the gold standard method for assessing malnutrition. Patients are given a score of A = well nourished, B = moderately malnourished or C = severely malnourished based on a nutritional history and physical exam (Detsky et al., 1987).

Sympathetic Nervous System – (med) Part of the autonomic nervous system that regulates involuntary function; sympathetic nervous system function is characterised by the 'fight or flight' responses such as raised heart rate, and increased blood pressure due to vasoconstriction.

Systematic Review – (stat) A structured, high level review of the literature on a given topic in which a specific research question has been formulated, inclusion criteria are specified and a methodology for data collection has been documented. In this sense a systematic review overcomes many of the biases of a narrative review process. A systematic review may or may not include a meta-analysis as part of the data synthesis. (Ng et al., 2006).

Thromboembolism – (med) Blockage of the bloodstream by a blood clot.

Variance – (stat) A measure of spread calculated by obtaining the sum of the squared deviations of the mean, divided by the number of means minus one. Alternatively, it is the square root of the standard deviation. Notated as s^2 (De Veaux et al., 2006).

Venostasis – (med) Abnormally slow blood flow.

Viscera – (med) The internal organs enclosed within a body cavity.

Voluntary knee extension – (nutr) Measure of peripheral muscle strength assessed with patients sitting erect and with the ankle fastened to a strain gauge, from which patient is asked three times, between one minute intervals, to extend the knee as far as possible (Henriksen et al., 2002).

Weighted mean difference – (stat) A summary statistic used for continuous variables in which differences between in means of an intervention are considered in terms of the sample size of the study from which it has been obtained. Abbreviated to WMD (Higgins and Green, 2006).

References cited within Appendix F - Glossary of Terms

Unless otherwise stated, all definitions and quotes have been sourced from Anderson, K. N., Anderson, L. E., and Glanze, W. D. (eds) (1998). Mosby's Medical, Nursing and Allied Health Dictionary, 5th edition. St Louis: Mosby.

Borenstein, M., Hedges, L., and Rothstein, H. (2007). Meta-analysis: Fixed Effect vs Random Effects.

Champe, P. C., and Harvey, R. A. (1994). Biochemistry, 2nd edition. Philadelphia: J. B. Lippincott Company.

Correia, M. I., and da Silva, R. G. (2004). The impact of early nutrition on metabolic response and postoperative ileus. Curr Opin Clin Nutr Metab Care **7**, 577-583.

De Veaux, R. D., Velleman, P. F., and Bock, D. E. (2006). Intro Stats, 2nd edition. Boston: Pearson Addison Wesley.

Detsky, A. S., McLaughlin, J. R., Baker, J. P., et al. (1987). What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr **11**, 8-13.

Egger, M., and Smith, G. D. (1998). Bias in location and selection of studies. BMJ **316**, 61-66.

Egger, M., Smith, G. D., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. Br Med J **315**, 629-634.

Evans, C., Galustian, C., Kumar, D., et al. (2008). Impact of surgery on immunologic function: comparison between minimally invasive techniques and conventional laparotomy for surgical resection of colorectal tumors. Am J Surg.

Everitt, B. S. (2002). Rank Correlation. In The Cambridge Dictionary of Statistics. London: Cambridge University Press.

Franz, M. J. (2008). Medical Nutrition Therapy for Diabetes Melitus and Hypoglycaemia of Non-Diabetic Origin. In Krause's Food and Nutrition Therapy, K. L. Mahan, and S. Escott-Stump (eds). St Louis, Missouri: Saunders Elsevier.

Galbraith, R. F. (1988). A note of graphical presentation of estimted odds ratios from several clinical trials. Stat Med **7**, 889-894.

Green, S., and Higgins, J. P. (eds) (2005). Glossary. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005].

Han-Geurts, I. J., Hop, W. C., Kok, N. F., Lim, A., Brouwer, K. J., and Jeekel, J. (2007). Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery. Br J Surg **94**, 555-561.

Han-Geurts, I. J., Jeekel, J., Tilanus, H. W., and Brouwer, K. J. (2001). Randomized clinical trial of patient-controlled versus fixed regimen feeding after elective abdominal surgery. Br J Surg **88**, 1578-1582.

Hancock, S., Cresci, G., and Martindale, R. (2002). The clear liquid diet: when is it appropriate? Curr Gastroenterol Rep **4**, 324-331.

Henriksen, M. G., Jensen, M. B., Hansen, H. V., Jespersen, T. W., and Hessov, I. (2002). Enforced mobilization, early oral feeding, and balanced analgesia improve convalescence after colorectal surgery. Nutrition **18**, 147-152.

Higgins, J. P., and Green, S. (eds) (2006). Analysing and Presenting Results. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. Section 8. In: The Cochrane Library, Issue 4Chichester: John Wiley & Sons, Ltd.

Huedo-Medina, T. B., Sanchez-Meca, J., Marin-Martinez, F., and Botella, J. (2006). Assessing heterogeneity in meta analysis: statistic or   index? . The American Psychological Association **11**, 193 - 206.

Jadad, A. R., Moore, A., Carroll, D., et al. (1996). Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? Controlled Clinical Trials **17**, 1-12.

Ng, T. T., McGory, M. L., Ko, C. Y., and Maggard, M. A. (2006). Meta-analysis in surgery: methods and limitations. Arch Surg **141**, 1125-1130; discussion 1131.

Plank, A. (2008). STA2300 Data Analysis Study Book, 2008.2 edition. Toowoomba: University of Southern Queensland.

Rodgers, A., Walker, N., Schug, S., et al. (2000). Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ **321**, 1493.

Russon, K., Findley, H., and Harclerode, Z. (2009). Peripheral Nerve Blocks - Getting Started (134). In Anaesthesia Tutorial of the Week, R. Hughes (ed). Rotherham, UK.: World Federation of Associations of Anaesthesiologists.

Schroeder, D., Gillanders, L., Mahr, K., and Hill, G. L. (1991). Effects of immediate postoperative enteral nutrition on body composition, muscle function, and wound healing. JPEN J Parenter Enteral Nutr **15**, 376-383.

Sobotka, L., Allison, S. P., Furst, P., Meier, R., Pertkiewicz, M., and Soeters, P. (eds) (2004). Basics in Clinical Nutrition, 3rd edition. Prague: Galen.

Whelan, K., Gibson, G. R., Judd, P. A., and Taylor, M. A. (2001). The role of probiotics and prebiotics in the management of diarrhoea associated with enteral tube feeding. J Hum Nutr Diet **14**, 423-433.

Wikipedia (2008). Overdispersion. web encyclopaedia: Wikipedia.

Wikipedia (2009a). Gortex. web encyclopaedia: Wikipedia.

Wikipedia (2009b). Statistical Dispersion. web encyclopaedia: Wikipedia.

Winkler, M. F., and Malone, A. M. (2008). Medical Nutrition Therapy for Metabolic Stress: Sepsis, Trauma, Burns and Surgery. In Krause's Food and Nutrition Therapy, K. L. Mahan, and S. Escott-Stump (eds). St Louis, Missouri: Saunders Elsevier.