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SCHOOL OF MEDICINE
DEPARTMENT OF SURGERY

A Multi-Centre Randomised Controlled Trial of Early Enteral Nutrition versus Standard Management in Patients undergoing Major Resection for Gastrointestinal Cancer

By

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Except where stated in the acknowledgements and in the text I declare that this thesis is my own work and based on research developed and conducted by me based in the Academic Department of Surgery, Cardiff University. The data was collected across 4 NHS Trusts in South East Wales.

Rachael C. Barlow

Signed.....
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DEDICATED TO MY HUSBAND ANDY,
MY DAUGHTER ELLIE (AGED 4 YEARS)
and SON EDWIN (AGED 1 YEAR)
FOR THEIR LOVE, SUPPORT and PATIENCE

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List of Abbreviations

BMI	Body Mass Index
ACTH	Adrenocorticotropic hormone
ADH	Anti diuretic hormone
APR	Acute Phase Response
ASA	American Society of Anaesthieology
BMJ	British Medical Journal
c	Centigrade
Chi	Chi squared test
cm	Centimetres
CMI	Cell mediated immunity
CNS	Central nervous system
CON	Conventional
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-reactive Protein
df	Degrees of freedom
DJ	Duodenojejunal
EEG	Electroencephalogram
EEN	Early Enteral Nutrition
EN	Enteral Nutrition
ENS	Enteric Nervous system
EORTC	European Organisation for Research and Treatment of Cancer
ERAS	Enhanced recovery after surgery
ETF	Enteral Tube Feeding
EU	European Union
FEV	Force Expiratory Volume
g	Grams
GALT	Gut Associated Lymphoid Tissue
GI	Gastrointestinal
GIT	Gastrointestinal Tract
GJT	Gastrojejunostomy tube
GMB	Gut Mucosal Barrier
HD	Handdynanometry
HEF	Home Enteral feeding
HRQoL	Health Related Quality of Life
IBW	Ideal Body Weight
IL-1	Interleukin-1
IL-6	Interleukin-6
IMN	Immunonutrition

IQ	Interquartile
IV	Intravenous
Kcals	Kilocalories
KG	Kilogram
l	Litre
LOHS	Length of Hospital Stay
m	Metres
MCRCT	Multicentred randomised controlled trial
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Maastricht Index
MMCs	Migrating Motor complex
MOF	Multi organ failure
MUMC	Mid Upper Muscle Circumference
N	Number of patients
NBM	Nil by Mouth
NCJ	Needle catheter jejunostomy
NCTN	National Cancer Trials Network
NG	Nasogastric
NGT	Nasogastric tube
NHS	National health service
NI	Nutrition Index
NICE	National Institute of Clinical Excellence
NJT	Nasojejunal tube
NPC	Non Protein Calories
NRI	Nutrition Risk Index
NRR	National Research register
NS	Non significant
NSAIDS	Non steroidal anti-inflammatory drugs
p	Significance
PEM	Protein Energy Malnutrition
PGID	Postoperative gastrointestinal dysfunction
PI	Principle Investigator
PNI	Prognostic Nutrition Index
RA	Research Assistant
RCT	Randomised Controlled Trial
REE	Resting Energy Expenditure
RNA	Ribonucleic acid
SD	Standard Deviation
SF-36	Short form 36
STD	Standard
t	Student t test

TIBC	Total-iron binding capacity
TLC	Total Lymphocyte Count
TNF-alpha	Tumour Necrosis Factor-alpha
TPN	Total Parenteral Nutrition
TSF	Tricep Skinfold Thickness
U	Mann Whitney U Test
U+Es	Urea and Electrolytes
UGI	Upper Gastrointestinal
UK	United Kingdom
ul	Microlitre
USA	United States of America
USS	Ultrasound sound scanning
WAG	Welsh Assembly Government
WCC	White cell count

John Reid Secretary of State for Health said in the House of Commons on 22nd March 2004;

"Investment in research saves lives"

Abstract

Background

The incidence of upper gastrointestinal cancer is increasing in the United Kingdom [1]. Radical resection of the tumour remains the most common curative intent treatment. Patients undergoing resections for malignancy are often malnourished [2-8].

Much research [5, 9-11] has indicated that malnutrition impedes surgical recovery. Therefore it would seem logical that the use of nutritional support may improve clinical outcome and aid recovery. There are two methods for delivering nutritional support, enterally and parenterally. Early enteral nutrition after major surgery has been advocated as an option for improving the clinical outcome of patients undergoing major cancer resections [12-16]. However, a meta-analysis [17] has suggested the current evidence is inconclusive. Traditionally, the majority of patients are starved for prolonged periods [18].

Aims

The aim of the randomised controlled trial presented in this thesis was to determine if early enteral nutrition, compared with the traditional management, improved clinical outcome.

Methods

Ninety-six patients were recruited in this analysis, over a 3-year period. There were 2 groups; one group received Early Enteral Nutrition (EEN group), which was delivered via a jejunostomy. The other group was managed with traditional, standard management (STD group), until it was deemed safe by the operating surgeon to commence oral diet and fluids.

Outcomes

The primary outcome of the trial was length of hospital stay. In addition, there were several secondary outcomes, including the development of major and minor complications, nutritional parameters, health related quality of life and a cost comparison.

Results

Median length of hospital stay for the standard group was 20 days (Range 14-28 days); and for the enteral nutrition group 16 days (Range 13-222 days) Mann Whitney U=822.5, p=0.021. Major complications were less frequent in the enteral nutrition group.

Summary of Results	STD group (N=42)	EEN group (N=54)	Test Statistic (p)
Length of Hospital (days)	20	16	U=822.5 (0.021)
Anastomotic leak % (N)	16.6 (7)	1.8 (1)	Chi= 6.73 (0.01)
Wound infection %(N)	28.5 (12)	5.5 (3)	Chi =16.3 (0.0001)
Chest Infection % (N)	21.4 (9)	9.3 (5)	Chi =6.03 (<0.05)

There were no statistically significant differences in health related quality of life between the groups. The enteral nutrition group EEN resulted in a cost saving of £1241 (£828-£5,315) per patient.

Conclusion

This was an early analysis of an ongoing trial. The results at present indicate that the use of Early Enteral Nutrition maybe clinically effective, maybe cost effective, and may reduce a patients' duration of hospital stay. However, full conclusions cannot be made until the close of the main trial.

Introduction

Upper Gastrointestinal Cancers (UGI) are a major cause of death in the UK accounting for approximately 19,000 deaths per annum [1]. Surgical resection of the tumour has long been considered to be the only hope of a cure [19]. Upper GI resection for malignancy is a major surgical procedure, and is associated with high morbidity and a well recognised in-hospital mortality rate [19-39].

Patients admitted for UGI resection are often malnourished [2-8]. Nutritional support remains the only modality capable of correcting and treating malnutrition [40]. However, traditional post-operative management of the patient after UGI resection often involves a prolonged period of 'nil by mouth', with only intravenous fluid therapy. Nutritional support is *ad hoc*, is often delayed and generally relies on parenteral nutrition (PN).

PN involves the delivery of nutrients directly into the systemic circulation, therefore bypassing the gastrointestinal tract (GIT). The use of enteral nutrition (EN) involves the delivery of nutrients via the GIT. It is hypothesised that EN may help to preserve GIT function and structure [41-45], having a central role in gut mediated immunity [46, 47]. Conversely, PN is associated with impaired GIT function and structure [48-51].

Studies have concluded that EN is superior to PN in improving clinical outcome [52-57] [58]. Length of hospital stay (LOHS) was reduced in the EN groups as compared to the PN groups in two RCTs [58] [52].

It is hypothesised that these benefits are further enhanced if EN is used immediately after the initiation of an acute phase response, for example after major surgery. Therefore, the use of immediate EN or early EN (EEN) seems optimal.

However, the benefits of EEN over standard post-operative management i.e. nil by mouth (typically for 7-10 days [59, 60]), has not been demonstrated adequately in clinical trials [17]. A meta-analysis [17] concluded that EEN might reduce the rate of post-operative infections and duration of hospital stay. This

analysis highlighted the problems with the previous trials, including small sample size, defective randomisation, varied methods of EN (jejunostomy, oral diet, oral supplements and nasogastric tube feeding), heterogeneous surgical procedures, and failure to evaluate the health related quality of life (HRQoL) of patients following discharge. They concluded that an adequately powered multi-centre randomised trial is necessary to assess EEN and standard management in patients undergoing elective GI surgery.

Furthermore, the only route for the delivery of EEN following radical upper gastrointestinal resectional surgery is into the small intestines below the newly formed anastomosis. There are two options, nasojejunal tube or feeding jejunostomy. Nasojejunal tubes have been shown to be unreliable and uncomfortable for patients [61, 62]. Feeding jejunostomy, is however an invasive procedure. Previous studies have reported major complication rates ranging from 0-40%, directly attributed to the feeding jejunostomy [63-75]. Therefore, the contemporary view is that the use of EEN should not become routine post-operative clinical practice, until proven safe, feasible and effective in improving clinical outcome in an adequately powered randomised controlled trial.

The aim of the randomised controlled trial presented in this thesis, is to compare the use of EEN versus standard post-operative management i.e. nil by mouth, taking into consideration the limitations with the previous trials.

Chapter 1 of this thesis is the literature review. It will commence with a review of the incidence, aetiology, symptoms and treatment options for the three types of UGI cancers studied in this thesis. The first section will end by detailing why this patient cohort was considered important for study.

The causes of malnutrition, along with the consequences of malnutrition, will be covered in the following section. Discussions as to why these issues are relevant for the patient undergoing major UGI resectional surgery for cancer will be described.

This will be followed by a review of the clinical studies on nutritional support in the surgical patient. However, it will be evident that the literature to date is inadequate to promote the routine use of enteral nutritional support in surgical patients.

Chapter 2 will contain the methods used in the randomised controlled trial (RCT) which forms the basis of this thesis.

Chapter 3 and 4 will present the results and discussion of the results in the context of the previous literature. Conclusions will be drawn and suggestions for further studies will be outlined.

1.0 Literature Review

The literature review will include the following,

1. A discussion of upper gastrointestinal (UGI) cancers, detailing the incidence, aetiology and treatment options for oesophageal, gastric and pancreatic cancers.
2. An overview of the incidence, causes and consequences of malnutrition. The consequences of malnutrition are wide ranging and include physiological and clinical consequences that may affect outcome in surgical patients.
3. The literature review will then explore the range of nutritional assessment techniques available to ascertain malnutrition.
4. The penultimate section will provide an extensive review of the clinical trials that have been conducted in the field of surgical clinical nutrition. The organisation of these trials into logical sections was difficult as there was variation in types of nutritional support delivered, by varying routes, to different groups of patients and varying choices of outcomes measures.
5. Finally, the literature review will debate the key components of high quality clinical trials. It will detail the frameworks available to ensure researchers conduct and report robust clinical trials.

1.1 Upper Gastrointestinal Cancers

1.1.0 Introduction

Cancer is a major contributor to death across the world. It is predominantly a disease of later life with more than 70% of cancers occurring in people over the age of 60 years [1].

Upper Gastrointestinal (UGI) cancers are common throughout the world. Each year, UGI cancers cause nearly 1 million deaths (World Health Organisation, 1998). The incidence and mortality of the different subtypes of UGI cancers are changing rapidly in many parts of the world. It is thought that environmental factors may be responsible for this. Social and cultural behaviour such as

smoking, alcohol, obesity, and social deprivation are contributory factors. Recent links with genetics are also being investigated and explored.

The incidence of cancer is increasing in the United Kingdom (UK). Cancer accounts for 28% of all deaths in males and 23% in females in 2003 [1]. Survival depends on the type of cancer, with five-year survival reported to be very low for cancers of the pancreas, lung, oesophagus and stomach. The range of survival for these cancers has been reported as 2-15% for patients diagnosed in England in 1998-2001 [1]. Colon cancer in contrast has a 5-year survival of around 50%, cancers of the bladder, cervix and prostate 53-71% and breast cancer (80%). However, overall survival has improved for most cancers in both sexes since the early 1990s [1].

The next section will summarise the epidemiology, incidence, aetiology, clinical features and treatment of UGI cancers. For the purpose of the thesis UGI will be considered to include oesophageal, gastric and pancreatic cancers.

1.1.1 Oesophageal Cancer

1.1.1.1 Epidemiology

Oesophageal cancer is the 7th most common cancer worldwide and accounts for 355,000 deaths annually (5.4% of all cancer deaths) [76] . Studies have revealed a wide geographical variation in incidence of carcinoma of the oesophagus. The highest incidence in the world is in China where it is the most common single cause of death accounting for more than 100 cases per 100,000 people per annum. Elsewhere incidence varies from less than five per 100,000 in whites in the USA to 26.5 per 100,000 in some regions of France [77].

In the UK, oesophageal cancers represent 1.9% of all cancers [78] . In the 1990s there were 7000 new cases of oesophageal cancers and 6,700 deaths reported per year. Incidence is rising both in the UK and worldwide [26]. This is particularly true for adenocarcinomas. Incidence is higher in men than women, with 12.6 men and 5.9 women per 100,000 presenting respectively per year in the UK [1]. Patients typically present with a mean age of 69 years for men and 75 for women [1].

Oesophageal cancer is the 9th most common cancer in men in Wales and 13th in women for the period 1993-2002 [79]. The incidence of oesophageal cancer in Wales is increasing; in 1993 a total of 334 patients were diagnosed, this increased to 443 people in 2003. The ratio of males to females was 1.44 in 1993 and 1.34 in 2003 [79]. Locally in Wales, Methyr Tydfil has the highest incidence for both males and females.

There has been a marked increase in the incidence of adenocarcinomas of the distal oesophagus and or gastric cardia which is thought to be a distinct disease entity [80] . Similarly, the incidence of squamous cell carcinomas has increased but this increase is not as dramatic as the increase for adenocarcinoma [80].

1.1.1.2 Aetiology

In the Western world alcohol is a major risk factor for oesophageal cancer [81, 82]. The mechanism by which it increases the risk of cancer is not known, however poor diet associated with increased alcohol consumption may be a factor, as well as the irritation of the mucosal lining leading to increased cell division and spontaneous mutation. Lack of fruit and vegetables with the subsequent lack of vitamin A, C and riboflavin are all associated with an increase in squamous cell carcinoma [83-85] .

Tobacco is also a major risk factor. Alcohol and tobacco appear to act in synergy to increase the rate of carcinogenesis [86]. Ingestion of pickled vegetables [87], increasing obesity, Barrett's oesophagus [88] and achalasia [89, 90] are all risk factors [91].

Oesophageal cancer is more common in areas of greater social deprivation [92], likewise 5 year survival has been reported to be better in patients from less deprived areas [93].

1.1.1.3 Clinical Features

Early oesophageal cancer may go unnoticed. Dysphagia is the most common symptom. Difficulty is initially experienced on swallowing solids, then semi-solids and finally liquids. Most cancers involve at least a 4cm length of the oesophagus

before diagnosis, and the typical patient will have had 3-6 months of dysphagia before first contacting a physician [94].

Therefore an inevitable consequence is a reduced dietary intake and subsequent weight loss. Weight loss, may be exacerbated by the metabolic effects of the tumour itself. Pain is uncommon and if it occurs is a late manifestation.

1.1.1.4 Surgical Resection for Oesophageal Cancers

Potentially curative resection involves resection of an appropriate length of the oesophagus along with any involved stomach and lymphatics. Restoration of continuation is typically achieved by the transposition of the stomach to form an oesophago-gastric anastomosis.

Several surgical options are available:

1. McKeown (1974) [22] developed a subtotal oesophagectomy performed through a midline incision and a right thoracotomy. In addition, a cervical incision is made to complete the cervical anastomosis. This is usually performed for cancers involving the upper oesophagus.

2. Ivor-Lewis (1946) [23] popularised an oesophagectomy technique involving a subtotal oesophago-gastrectomy performed through a midline incision to enable mobilisation of the stomach. Typically resection involves removal of about one fifth of the stomach. In addition, a right thoracotomy is performed providing access to the oesophagus to complete the anastomosis. This became known as the Ivor-Lewis oesophagectomy.

3. The Transhiatal oesophagectomy was popularised in the USA and Brazil by Orringer in the mid 1980s [24, 25]. It involves opening the abdomen through a midline incision (without thoracotomy) and the oesophagus is resected in the chest through the diaphragmatic hiatus. Stomach or colon for reconstruction is then passed through the posterior mediastinum to the neck where it is anastomosed to the upper oesophagus through a cervical incision [26]. This is typically used for cancers of the lower oesophagus.

4. Over the past few years minimally invasive oesophagectomy using endoscopic instruments has been introduced into oesophageal cancer surgery. This

procedure is used for early tumours and performed by endoscopic mucosectomy or mucosal ablation techniques [95].

Patients after oesophagectomy are prone to developing major complications, which include: haemorrhage, infection, thromboembolic disease and cardiovascular problems. Pulmonary complications may range from a simple chest infection to pneumonia, pulmonary collapse, persistent pneumothorax, haemothorax or damage to the trachea or bronchus. Extensive lymphadenectomy can affect pulmonary lymphatic drainage, which can predispose to pulmonary oedema [27-38]. Anastomotic leak is a serious complication post-operatively; it can be attributed to a technical error if it develops within 72 hours post-operatively. According to UK guidelines the incidence of anastomotic leak ideally should not exceed 5% for UGI resections [39]. Other complications such as chylothorax (occur in 2-3 % of resections), laryngeal nerve palsy and anastomotic strictures are also often reported. Hospital mortality should be less than 10% [19].

Prognosis is dependent on the depth of invasion of the tumour (T stage), the presence of nodal metastases (N stage) and the ratio of involved to removed lymph nodes. Five-year survival is reported to be 5-10% [19].

1.1.1.5 Adjuvant, Neo-Adjuvant Chemotherapy and Chemoradiation

Evidence supporting the use of adjuvant chemotherapy is limited [19]. However, the use of neo-adjuvant chemotherapy was studied by the MRC Oesophageal Working Party (OE02 study) in 2002 [96]. The authors concluded that neo-adjuvant chemotherapy, i.e. 4-cycles of cisplatin and 5-fluorouracil every 3 weeks followed by surgical resection was superior to surgery alone in improving two-year survival. Following this study, it was recommended that neo-adjuvant chemotherapy be used for all operative patients with the exception of T1 stage tumours to improve survival. However, a Cochrane review by Malthaner *et al* (2006) [97] of eleven randomised trials involving 2019 patients, concluded that preoperative chemotherapy plus surgery may offer a survival advantage

compared to surgery alone for resectable thoracic oesophageal cancer, but the evidence remains inconclusive.

The use of chemoradiation in improving survival was suggested in a retrospective study by Crosby *et al* (2004) [98]. The authors concluded that definitive chemoradiation for inoperable oesophageal cancer led to a median overall survival of 26 months, with advancing stage of disease correlating positively with prognosis. Interestingly, a subgroup analysis of patients who did not proceed to resection secondary to co-morbidities rather than tumour stage had a median survival of 40 months. The results of this study indicate that the use of definitive chemoradiation may lead to a similar survival rate as resectional surgery with curative intent.

A French study, Bedenne *et al* (2007) [99] of patients with potentially curative, operable thoracic oesophageal cancer (stage T3N0-1M0). Patients received two cycles of cisplatin and 5-fluorouracil and concomitant radiotherapy. Patients, who responded to this regimen, were then randomised to either surgery or additional chemoradiation. The authors concluded that there were no differences in survival at two years between the two randomised groups. This study did not evaluate health related quality of life.

There is no consensus to suggest that radiotherapy in isolation is beneficial in oesophagectomy patients [100].

1.1.2 Stomach Cancer

1.1.2.1 Epidemiology

Gastric cancer is one of the prominent causes of death from malignant disease [101]. The incidence worldwide is 11 people per 100, 000 (World Health Organisation, 1998). There are wide international variations in incidence. It is common in Japan, South America and Eastern Europe, occurs with intermediate frequency in Western Europe, and is uncommon in the USA. In addition to international variations, the incidence varies within countries (World Health Organisation, 1998).

It is primarily a disease in the older adult with over 80% of patients presenting being over 65 years [102]. The incidence is twice as high in males as females [101].

Gastric cancer is relatively common in the UK, with a reported incidence of 15/100,000 people per annum in 2004 [19]. It is reported that there are 10,000 new cases and 7,500 deaths per annum.

Incidence is correlated with low socio-economic status. In the UK, the areas with a high incidence include South Wales, Scotland and the Midlands. The incidence in Wales, of stomach cancer, is however falling [79].

Males have a higher incidence than females, with new cases reported as 420 for males and 247 for females per annum in the UK [19]. The mortality rate from gastric cancer in Wales, however, exceeds that of the UK. With 34 deaths per 100 000 males, compared with 23 deaths per 100 000 reported in the UK [79].

Delays in diagnosis are common, and as many as one in three patients in Britain continue to present with advanced, incurable disease. Survival has improved over the past 10 years in Wales, with one-year survival reported as 33% for the period of 1995-1999 [79]; compared to 1990-1994 when it was 25.78%.

1.1.2.2 Aetiology

The aetiology of gastric cancer is multifactorial. There are a few definite pre-malignant conditions and risk factors. These include: a gastric polyp, pernicious anaemia [103, 104], autoimmune and environmental gastritis, gastric surgery

[104] for benign conditions, gastric mucosal dysplasia, cigarette smoking, long standing dyspepsia and genetic factors.

Dietary factors may also be important. A reduced intake of fresh fruit and vegetables, leading to a reduced intake of carotene, vitamin C and E are risk factors [105]. Dietary nitrates and nitrites, and excessive salt intake [106] are also linked [105]. In 1994, WHO declared Helicobacter pylori [107-109] to be a Grade 1 carcinogen for gastric adenocarcinoma and mucosa associated lymphoid tumours of the stomach [110]. The incidence of cancer of the stomach is increased in first degree relatives of patients [111].

1.1.2.3 Clinical Features

There has been a change in anatomical distribution with an increasing trend for tumours to be located in the proximal stomach and cardia [112, 113] [114] as opposed to the distal stomach.

It is a difficult disease to diagnose early, because of the time lag between the commencement of the growth, and the appearance of symptoms, and also because of diversity in its presentation. Yet, the key to improving the outcome of gastric cancer is early diagnosis [105].

1.1.2.4 Gastric Surgical Resection

For those patients who are fit enough, surgical resection is the only option for a cure in gastric cancer. The extent of the disease at presentation determines the extent of the resection. It is reported that in the West, patients often present late with gastric cancer, and hence the cure rate is low [115].

The two most appropriate operations for gastric cancer are a radical subtotal distal gastrectomy for the lower one third of the stomach and a total gastrectomy for tumours of the middle and upper third.

Studies in Japan have demonstrated improved survival if patients undergo a D2 or 'systemic lymphadenectomy' or D3 'extended lymphadenectomy' [116].

1.1.2.5 Neo adjuvant chemotherapy in stomach cancer

In the past, the role of adjuvant therapy for gastric cancer was indefinite. However, two randomised controlled trials have shown the survival benefit of adjuvant oncological treatment. The Amercan Intergroup (0116 trial) [117] concluded that adjuvant chemoradiation therapy prior to resection was superior to surgery alone. The European MAGIC trial [118] showed improved survival and disease-free survival with pre-operative chemotherapy epirubicin, cisplatin, and 5-FU (ECF) given every 3 weeks pre- and post-operatively compared to surgery alone.

1.1.3 Pancreatic Cancer

Pancreatic cancer remains one of the major challenges in surgical oncology, it is termed 'the Everest of solid tumours' and challenges the whole of the multi-disciplinary team [119].

1.1.3.1 Aetiology

Little is known about the aetiology of pancreatic cancer [120]. However, tobacco smoking is associated with a doubling of the risk of pancreatic cancer, accounting for 30% of cases [121-130].

Other aetiological factors have been suggested. These include, a limited consumption of fruit and vegetables [131], alcohol, high protein and fat diets, high coffee consumption, diabetes mellitus, pernicious anaemia and previous gastric surgery [132]. Chronic pancreatitis is thought to be a pre-malignant condition, increasing cancer risk by 5-15 fold [129, 133]. Genetic links have also been reported [134-142]. Recently, certain occupational groups such as chemical and petrochemical, dye and rubber industry workers are thought to be at greater risk [143].

1.1.3.2 Incidence

Carcinoma of the pancreas remains a deadly disease [79]. Incidence has increased over recent decades, and is highest in Western countries. Approximately 7,200 new cases of pancreatic cancer are diagnosed per year in the UK and Ireland [1, 144]. For the period of 1992-2002 the incidence of pancreatic cancer has remained stable. Pancreatic cancer is predominantly a disease of the elderly with 80% of cases reported in patients aged 60-80 years [145] [146] . The rate of pancreatic cancer is higher in men than women generally in the UK. In Wales, however, the incidence is similar in men and women with 202 males diagnosed per annum in Wales and 220 females [79].

Pancreatic cancer has a very poor prognosis and has the lowest survival amongst all the UGI cancers. One year relative survival is 13.60% for 1990-1994 and 14.11% from the period of 1995-1999 [79].

1.1.3.3 Clinical Features

The most common type of pancreatic cancer is ductal adenocarcinoma, which accounts for over 90% of all tumours. Eighty to ninety percent of tumours present in the head of the gland but metastasis is common [147]. There are also many other rare types of endocrine and exocrine tumours [132].

1.1.3.4 Surgical Resection

The most common surgical procedure is Pylorus Preserving Pancreaticoduodenectomy (PPPD). Five-year survival is poor approximately 10% post procedure [148, 149]. There are also more radical surgical options available such as total pancreactectomy and portal vein excision [150-152]. The surgical resection is complex and it is not uncommon in spite of adequate preoperative staging, to discover at open laparotomy distant metastases or local spread, which preclude the operation proceeding. Complication rates of resectional surgery are high when compared to other operations [153], although mortality rates have fallen. Reoccurrence of the tumour even after curative intent surgical resection is common [153].

1.1.4 The Management of Upper Gastrointestinal Cancers

The patients presenting with UGI cancers are, by and large, elderly. They typically present with multiple pre-existing co-morbidities, this contributes to the risks for undergoing resectional surgery [20, 21].

The presence of the underlying cancer produces immunological, physiological and metabolic consequences, often rendering the patient debilitated. Particularly there may be nutritional inadequacies. Some patients may have received neo-adjuvant chemotherapy, which may compromise a patient's nutritional and immunological status prior to surgery. All these factors will be discussed later in the literature review.

Operations with curative intent for UGI cancers are prolonged and technically demanding. They involve extensive dissection of the tumour and often-complex reconstruction. There is the potential for rapid blood loss, intraoperative cooling and fluid shifts.

Post-operatively, conventional management has involved a prolonged period of 'nil by mouth' until the integrity of the newly formed anastomosis is confirmed radiologically. The use of this practice, in conjunction with the complex metabolic, endocrine and neuroendocrine responses, affect fluid balance, insulin resistance and pain. All these complicate and intensify the complexity of post-operative recovery in these patients. Maintenance of systemic circulation and ventilation are complex post-operation, and these patients tend to be managed on critical care units.

Of all the elective complex major operations, the procedure of resections for UGI cancers are associated with the highest risk of septic related complications and mortality [154]. Nutrition has long been reported to influence clinical outcome [155]. Any treatment that can potentially improve clinical outcome, whilst improving quality of life, is beneficial. However despite this, the nutritional management of these patients' remains an area of controversy, with some studies showing evidence of benefits from perioperative nutritional support and others showing no or an equivocal effect. These will be discussed at length in section 1.6.

1.1.5 Summary of Section

Cancer is a major contributor to death across the world with UGI cancers accounting for 1 million deaths worldwide.

This section has provided an overview of the increasing incidence of UGI cancers both across the UK and locally in Wales. The aetiological factors for the development of UGI cancers are diverse with nutritional factors being stated as central to the disease origin.

What is apparent is that UGI cancers have clinical consequences which impact directly on patients' nutritional status and food intake.

Coupled with the treatment modalities of surgery and chemotherapy, it is inevitable that patients with UGI cancers are at risk of developing malnutrition. Thus the next section will detail the physiological and clinical manifestations of malnutrition. It will also outline the causes and incidence of malnutrition in particular relating to the surgical patient.

1.2. Malnutrition: Incidence and Causes

1.2.0 Introduction

Malnutrition has long been considered to have an adverse effect on the surgical outcome in patients with benign and malignant disease. In 1936, Studely [9] highlighted the relationship of pre-operative weight loss and surgical outcome. Patients who had lost more than 20% of their usual body weight prior to surgery suffered a 33% mortality rate. This was compared to 4% mortality in patients with a weight loss between 15% and 20%. The conclusion, from this study, was that a weight loss exceeding 15-20%, deleteriously affected surgical outcome, and prognosis. Subsequently, much evidence has been published identifying the effects of malnutrition on physiological outcome.

This section will review the literature regarding the extent, causes and consequences of malnutrition in hospital patients, with an emphasis on surgical patients.

1.2.1 The Extent of Malnutrition

Malnutrition literally means bad, or faulty, nutrition. It is an 'umbrella' term, encompassing all types of nutritional disorders such as obesity, macronutrients and micronutrient deficiencies. There is no consensus definition of malnutrition. For the purpose of this thesis, however, malnutrition will be defined as:

> *"A state in which a deficiency of nutrients such as energy, protein, vitamins and minerals causes measurable adverse effects on body composition, function and clinical outcome."*

Stroud (2006) page 3 [40]

Malnutrition is a public health problem, affecting 5% of the total population in the United Kingdom [102, 156]. Florence Nightingale, in 1859, was one of the first to draw attention to the problem of malnutrition in hospitals. She reportedly stated

that patients are often 'Starved in the midst of plenty' [157]. Yet, nearly 150 years later, malnutrition in hospital is still a major cause for concern [40]. A systematic review, by Stratton *et al* (2000) [158], re-analysed many of the studies published reporting the percentage of patients with malnutrition in the general hospital population. The incidence of malnutrition varied from 5-64% depending on the criterion used to define malnutrition. Theses studies are summarised in table 1.2.1.

Table 1.2.1 Studies published to date using standardised anthropometric criteria to determine incidence of malnutrition in surgical patients

Author	Criterion	Percentage of patients
Anderson *et al* (1984) [159]	BMI < 20 Weight Loss > 4.5 kg	30
Kamath (1986) [160]	Low albumin, Hb or TLC	58
Corish and Kennedy (2000) [161]	BMI <20	16
Larsson *et al* (1994) [162]	Weight loss >10%	29
Kyle (2001) [163]	BMI <18 kg m2 Index of fat free mass A combination of anthropometric indices	9 31 11-45
Naber *et al* (1997)[164]	NRI moderate or high risk	57
Audivert (2000) [165]	BMI <28 kg m2 A combination of anthropometric indices below 15th centile	33
Braunschweig *et al* (2000) [166]	All these studies used a combination of anthropometric, biochemical and or immunological indices	20-58
Landi (2000) [167]	Comparison with IBW BMI<21.7 kg m2	16.2 27.3
McWhirter and Pennington (1994) [163, 168-171]	BMI 20 kg m2 and TSF or MAMC <15th centile	40
Harrison *et al* (1997) [172]	A variety of nutrition risk scores	50-64

(BMI= body mass index; IBW- ideal body weight; kg= kilograms;
Hb= haemoglobin; TLC=total lymphocyte count; NRI= nutrition risk index)

Cancer, increases the risk of malnutrition [4, 173]. The type and site of the tumour, stage of disease, and the treatments performed all affect the extent of malnutrition in cancer patients [174]. The reported incidence of malnutrition for

gastrointestinal (GIT) surgical patients, with benign disease, ranged from 6% [175] to 87% in patients with GIT cancer [2-8].

A summary of the studies that reported the incidence of malnutrition in cancer patients is presented in table 1.2.2.

Table 1.2.2 The Incidence of malnutrition in Gastrointestinal Cancer Patients

Author (year)	Incidence	Criterion used to Define Malnutrition
Persson *et al* (1999) [8]	80% UGI cancers	Subjective Global Assessment (SGA)
DeWys *et al* (1980) [176]	Pancreatic cancer 83% Oesophageal cancer 87% Gastric cancer 65%	Weight loss > 5% in 6 months
Riccardi and Allen (1999) [94, 177]	UGI cancers 70%	10% weight loss over 4 months
Daly *et al* (2000)[177]	Oesophageal cancer 57%	Involuntary weight loss
Martin *et al* (1999) [178]	Oesophageal Cancer 58%	Involuntary weight loss
Saito *et al* (1990) [179, 180]	Oesophageal Cancer 81.2% Gastric Cancer 64%	Abnormal levels of at least one of: body weight, TSF, MAMC, albumin
Rey-Ferro *et al* (1997) [181]	Gastric Cancer 63%	NRI less than 97.5
Larrea *et al* (1992) [182]	Oesophageal Cancer 78.9%	Not reported
Sitges-Serra *et al* (1990) [183]	N=84 Oesophageal Cancer 58%	TSF below 5th percentile Albumin >35g/l, involuntary weight loss
Thoresen *et al* (2002)[184]	N=46 GI cancers 83%	Unintentional weight loss
Belghiti *et al* (1987) [185]	N=24 GI cancers 63%	Weight loss > 10%
Bozzetti *et al* (1989) [186]	N=14 GI cancers 30%	BMI >18

(NRI-nutrition risk index; TSF-Tricep skinfold thickness; BMI body mass index; MAMC-mid arm muscle circumference)

To summarise so far, malnutrition is thought to affect 5% of the total population with the incidence increasing to between 9-58% in hospitalised patients and

increasing to 58%-90% in patients with UGI cancers. The negative impact of malnutrition on surgical outcome has long been considered.

1.2.2 Causes of Malnutrition in the Surgical Patient

This section will outline the causes of malnutrition in the surgical patient with cancer. The causes will be classified into cancer related factors, surgical related factors and lack of nutritional support.

1.2.2.1 Cancer Related Factors

Anorexia

Anorexia or loss of appetite is a prominent clinical feature of acute or chronic disease. It is thought to be responsible for malnutrition in 15-40% of upper gastrointestinal (UGI) cancer patients, at presentation [187].

It seems ironic that anorexia often occurs when the body's' energy requirements are elevated i.e. in response to an acute phase response, however, the affect of anorexia can either be deleterious or beneficial, depending on the timing, onset and duration of the anorexic period.

The initiation of anorexia may be based on evolution. Does anorexia, and hence the reduction in the 'hunger' feeling, eliminate the necessity to search and scavenge for food? This may limit the energy expenditure from heat loss, from bodily movement, and also reduces the risk of further harm to occur, when the individual is incapacitated as a result of infection or injury. Following on from this theory, animal studies have suggested that 'force feeding' is detrimental in the short term, inducing infective complications [188].

However, prolonged anorexia, will inevitably lead to starvation and malnutrition, the consequences of which are described later in this chapter.

The physiological origins of anorexia are complex. Pro-inflammatory cytokines are central in the development of anorexia. The cytokines, Interleukin-1 (IL-1),

Tumour necrosis factor-alpha (TNF-alpha)[189], IL-6 [190], interferon [191] and IL-8 [192] are reported to be released in response to the presence of microbial products. These subsequently activate monocytes and macrophages, through surface proteins such as CD11B and CD14. Also, cytokines in particular IL-1 alpha and beta, are thought to target central and peripheral nervous system phenomena, these include:

1. The hypothalamus-feeding centre and activation of the pituitary-adrenal axis.

2. The prostaglandin dependent mechanisms;

3. The modifications of neurotransmitter production;

4. The gastrointestinal tract (leading to inhibition of gastric motility, decreased gastric emptying, and modulation of intestinal motility

5. Endocrine response (affecting corticotrophin releasing factor, cholecystokinin, glucagon and insulin)

Malhotra and Bird (1997) and Chang and Bistrian (1998) [193, 194]

Other possibly factors leading to anorexia in cancer patients are altered intestinal enzyme production, GIT motility and a feeling of fullness often attributed to delayed gastric emptying [195]. Iniu *et al* (1999) have also linked leptin and satietins to altered appetite and anorexia [199].

Changes in taste and smell perception, psychological factors, uncontrolled pain and therapy induced side effects all play a role in the aetiology of anorexia [196]. Taste changes, are often reported in cancer patients [195]. In particular, patients report a hypersensitivity to sweet flavours and bitter foods. This is thought to be secondary to the high concentrations of amino-acids, purines and polypeptides in the brain [195].

Dysphagia
Riccardi and Allen (1999) [94] reported malnutrition in 70% of patients with UGI cancer cases on presentation. In most cases, weight loss was rapid, occurring over a period of less than four months. The main cause was progressive dysphagia, pain and/or anorexia. A similar review [197], suggested that dysphagia in patients with gastric or oesophageal cancers is the main determinant of malnutrition. Dysphagia in UGI cancer patients is usually the result of obstruction by the tumour, physically preventing food from entering the stomach.

Increased Energy Expenditure
Cancer may increase energy expenditure [198]. A study in rats demonstrated that transplanted tumour cells increased resting energy expenditure (REE) by 40% [199].

In humans, patients with pancreatic cancer, had a higher REE (33 % higher) when compared to individuals without cancer [200] [201-203]. Other studies have also reported a higher REE (increased by 138-289 calories/day) in cancer patients [196, 204, 205]. Once again leptin secretion may have an impact on energy expenditure [199].

1.2.2.2 Surgical Factors

The Acute Phase Response (APR)
Surgery, like any injury to the body elicits a cascade of reactions termed the acute phase response (APR). This 'stress' response was first described in 1932 [206, 207]. Subsequently, the endocrine aspects of the response were described in 1959, by Egdahl [208].

Recent understanding of cytokines has provided further insight into the complex mechanisms that initiate the APR. Cytokines are produced from activated leucocytes, fibroblasts and endothelial cells at the site of the injury. Among the initial cytokines released are IL-1 and TNF–alpha [209]. Within 30-60 minutes, these cytokines stimulate the production of IL-6, becoming sufficient in concentration after 2-4 hours, to stimulate the release of hormones-ACTH, ADH,

and cortisol. These then lead to the cascade of hypercatabolism resulting in the catabolism of glycogen, adipose and muscle proteins.

C-reactive Protein (CRP), fibrinogen and other anti-proteinases are released following the serum changes in IL-6 and the APR [210, 211]. One study correlated circulating level of IL-6 to the severity of the surgical procedure [209]. Major GI surgical procedures produce one of the greatest increases in IL-6 production post-operatively [212]. If complications do not occur, the IL-6 levels typically start to decrease within 48-72 hours of the surgical procedure. IL-6 is considered a useful indicator of the overall APR as it correlates with hepatic production of acute phase response proteins and inversely with liver proteins such as albumin and transferrin [212].

Starvation after Surgery

It is traditional practice to withhold food, nutrients and oral fluid in the immediate post-operative period. This 'starvation' after surgery has a different metabolic response to that observed in 'simple' starvation. The two responses are summarised below.

The metabolic response to 'simple' starvation is aimed at the conservation of body tissues, whilst maintaining a constant supply of energy substrates to the vital organs. Basal metabolic rate is reduced. The complex physiological mechanisms and hormonal regulation lead to a reduction in insulin production, and a subsequent rise in glucagon production. The result is an increase in glycogen degradation with subsequent glucose release. After depletion of glycogen stores, protein and lean body tissues are converted to glucose by gluconeogenesis. Fatty acids, derived from the degradation of adipose tissue, produce an essential supply of ketones for utilisation by the brain for energy. It is this rise in ketones in the blood that 'triggers' the reduction in gluconeogenesis, leading to conservation of lean body mass preserving vital organ mass and organ function.

Healthy individuals can sustain extended periods of 'simple' starvation without permanent harm, because of these adaptive metabolic responses. However periods of starvation, after surgery or when the patient is 'stressed', are not

characterised by the same metabolic response. On the contrary, starvation in the stressed patient, in the presence of an acute phase response, is characterised by an increased basal metabolic rate. At the same time, the process of ketogenesis and the subsequent production of ketones fail to suppress gluconeogenesis, and hence protein degradation and lean body mass is accelerated. Thus, starvation in a stressed patient leads to accelerated tissue loss and organ function, and impending malnutrition.

Insufficient Utilisation of Ingested Nutrients

Patients post-operatively develop a sequence of events similar to that seen in Type II diabetes. Patients develop insulin resistance. Patients therefore become 'inefficient' and unable to utilise nutrients at the cellular level. Much research has focused on this over the last decade and is summarised in a review paper [213].

Maldigestion and Malabsorption

The normal GIT has an maximal absorptive capacity of 4500-7000kcals/day [214]. Pancreatic exocrine function is impaired in malnutrition, which inevitably leads to maldigestion and absorption [215]. Coupled with this, bacterial overgrowth and malnutrition can alter GIT motility and enzyme production [216], leading to malabsorption [217]. The overzealous use nutrition delivered into the GIT at this time may overwhelm the digestive and absorptive capacity of the GIT. If macronutrients delivered via the nutrition are not absorbed in the small intestines, they are subsequently fermented in the colon, causing diarrhoea [217]. Therefore the delivery of nutritional support in malnutrition requires specific attention.

1.2.2.3 Lack of Nutritional Support

The use of nutritional support for patients undergoing major surgery is not routine in the peri-operative period. Standard post-operative management is to withhold oral diet and oral fluids ('nil by mouth'), and maintain hydration status with the prescription of intravenous fluids, until the surgeon decides that oral diet and fluids can resume.

Butterworth *et al* (1974) [218] identified a number of reasons accounting for the suboptimal delivery of nutrition in surgical patients in hospitals. The reasons were:

1. The diffusion of responsibility of patient care between members of the multidisciplinary team

2. The failure to observe and monitor patient's food intake

3. The withholding of meals because of diagnostic tests

4. The failure to recognise increased nutritional needs as a result of injury or illness

5. The failure to provide nutritional support after surgery and failure to appreciate the role of nutrition in the prevention and recovery from infection

6. The prolonged use of 'nil by mouth' and glucose and saline intravenous fluids in the post-operatively phase.

This study was conducted over 30 years ago. Many of the reasons highlighted are still issues of concern in UK hospitals today [40].

An audit in 1996 [1] found that the mean duration 'nil by mouth' in adult gastrointestinal surgical patients was 10 days (range 1-40 days) in a Teaching Hospital. The clinical rationale for this practice was based on assumptions that the delivery of nutrition post-operatively was not safe, or clinically indicated, in the post-operative period.

1

219. Barlow, R., *An audit of the length of time patients are starved on a Surgical Unit in a Teaching hospital.* 1996, Cardiff and Vale NHS Trust.

Since this, one published survey [220] and one unpublished survey [2] found that nutritional support practices for patients undergoing resection for upper gastrointestinal malignancy, across the UK post-operatively were *ad hoc*. The authors attributed this practice to the lack of robust clinical trials performed, and the subsequent lack of consensus as to what is the optimal modality for providing nutritional support (if at all), peri-operatively.

1.2.3 Summary of Section

The cause of malnutrition in patients undergoing surgery for cancer is multifactorial. This section has subdivided them into cancer related such as anorexia, altered metabolism and dysphagia; surgery related such as the acute stimulation of the inflammatory and acute phase response. Coupled with this is the post-operative starvation associated with the traditional management of patients following surgery.

The next section will discuss methods of assessing nutritional status and determining malnutrition.

2

59. Barlow, R., *A survey of Peri-operative nutritional practices in NHS Trusts across the UK.* 2003, Cardiff and Vale NHS Trust.

1.3 Nutritional Assessment

1.3.0 Introduction

Many anthropometric, biochemical, immunological tests and body compositional analyses have been developed to assess patient's nutritional status. However, no single parameter can fully characterise the extent of malnutrition, as there is currently no one anthropometric measurement that is considered to be completely reliable, as well as practical for use in the clinical setting. More precise techniques such as measurements of total body potassium or sodium or dual energy X-ray absorptiometry are not practical for use in the clinical area, being too cumbersome for use outside the laboratory research setting.

This section will detail the practical methods available for nutritional assessment of the surgical patient in a clinical setting, which are suggested to enable a reliable and effective nutritional assessment.

1.3.1 Weight

Body weight is the most practical and simple measure of the total body components. The measured weight can be compared with ideal and desirable weight ranges and previous weight [221]. However, body weight is not an accurate guide to depletion of body stores, so other measurements should be used.

1.3.1.1 Percentage Weight Loss

The use of percentage weight loss is essential as this may indicate the extent or duration of any underlying disease. Studely (1936) [9] indicated that surgical outcome was influenced by pre-operative percentage weight loss. This was also the finding of Roy *et al* (1985) [222], who found that weight loss of >6% of usual body weight accurately predicted morbidity and mortality in surgical patients. The accuracy of the prediction, does however, depend on the accuracy of the original weight before the onset of weight loss. Many patients can give some estimate of their weight when well, but the accuracy of this reported weight is questionable [223]. Nonetheless, various national reports, organisations and individual workers have provided a range of cut off values, which generally fall within the 5-

10% range of weight loss over the previous 3-6 months [224-226]. There is a paucity of information as to why these cut off values were chosen, but it seems that clinical judgment was important.

1.3.1.2 Body Mass Index

The relationship of weight with height is also useful, as body size dictates expected body weight. The most commonly used index is the Quetelet index (1869), usually known as the Body Mass Index (BMI) [227]. It is calculated by dividing weight (kg) by height squared (m). Both weight and height measurements are non-invasive and relatively easy to obtain in healthy adults, however, older people may present with numerous medical and physical problems, making these measurements more difficult to obtain. For example, it is often impossible to measure accurately in the elderly due to mobility problems and kyphosis or scoliosis. In this situation measurements of other body segments can be used as an alternative. These include: knee height [228] which relies on measuring long bones that do not lose length over time in the same way as the spine.

BMI indicates chronic protein and energy status, whereas percentage weight loss indicates acute changes in protein and energy status. The usefulness of BMI is limited by poor sensitivity with respect to baseline assessment, particularly for overweight patients who can undergo significant change in nutritional status. Furthermore, co-morbid conditions that promote underhydration, oedema or ascites will confound the calculation [229, 230].

1.3.2 Determination of Body Stores

The loss of skeletal muscle is an important clinical indicator. The skeletal muscle mass constitutes 15,000 to 20,000 stored calories. A study [230] in surgical patients, illustrated that patients who have lost 30% of their total protein stores have visible tendons which are prominent for palpitation, additionally, the bony prominences of the scapula are evident.

Skeletal muscle mass can degrade by 50-70% in severe malnutrition. Mid upper arm circumference (MUAC) is used to calculate mid upper muscle circumference (MUMC). This is used as a prediction of skeletal muscle reserves, and thus, an indication of residual amino acids source, available for times of stress and starvation.

Twenty-five to sixty percent of total body fat is located subcutaneously. Body fat can provide 50,000 to 140,000kcals in an adult. Gross loss of body fat can be observed, not only from the patients' appearance, but also by palpating skinfolds between the thumb and finger. If the dermis can be felt a study revealed that this correlated with a percentage body fat of less than 10% [230, 231].

In addition, body fat estimation can be gained from measuring Tricep Skinfold Thickness (TSF) with skin calipers. Work has shown that TSF correlates well with total body fat [231]. However another study failed to demonstrate this correlation in severe malnutrition, presumably because of an abnormal distribution of fat [232].

In general, for all arm anthropometry, if measurement falls below the 10th percentile, it provides an indication of malnutrition or increased risk of developing complications. The most commonly used standards for triceps skinfold thickness and mid arm circumference are those reported by Jellife in 1966 [233]. However these are based on measurements of European male military personnel and low-income American women which are not considered representative of the general UK population, comparison and interpretation needs to be made with caution.

Interpretation of the data may be further limited by inter-rater variability. Hall *et al* (1980) [234], found inconsistencies when three different observers performed anthropometric measurements. The coefficient of variation was 4.7% for arm circumference and 22.6% for triceps skinfold thickness. Also, the time frame needed before changes in measurements reliably reflect alterations in physiological condition must also be considered as this is typically based on the assessor clinical judgment.

1.3.3 Skeletal Muscle Function

The function of muscle is also an important clinical indicator [235]. Handgrip strength or Handdynanometry is a quick and easy objective test to perform. It measures the muscle function of the hand and arm. Its usefulness is limited however by the need for patient cooperation and the need to avoid use of analgesics and sedatives which impair patient response [229]. Changes in muscle function may precede body composition changes and may serve as an indicator of functional impairment at subclinical levels. Work from the Minnesota Experiments [236] studied healthy men over a 3 month period and showed that a 10% weight loss over 3 months lead to a reduction in handgrip strength by 8-10% and this correlated with a reduction in physical strength. Research has shown that grip strength correlates well with indicators of muscle mass, such as mid-arm muscle circumference and creatinine-height index [237]. Several investigators have proposed hand grip strength as an indicator of malnutrition[235, 238] . All investigators recognise that handgrip alone is not sufficient to identify malnutrition; it needs to be used in conjunction with other indicators. However, Klidjian *et al* [237] did suggest that grip strength, alone, can be used as a predictor of malnutrition and used as a screen to identify patients in need of further assessment.

Hand-grip strength has also been demonstrated to be a useful test to predict post-operative complications in surgical patients [239] [240, 241] .

Windsor and Hill (1988) [242] correlated hand grip strength with body protein levels. They concluded handgrip strength was superior to biochemical and anthropometric markers in the determination of malnutrition. This was also the findings of the study by Klidjian *et al* (1980) [237]; this study examined 225 patients admitted for elective surgery and found that grip strength was a more sensitive indicator than weight loss, BMI, skinfold thickness, MUAC and serum albumin in predicting post-operative complications. They demonstrated that 29 out of 44 patients who had grip strength less than 85% of normal developed post-operative complications whereas only 3/58 (5.1%) patients, who had pre-operative handgrip strength above 85% of normal, developed complications.

Two studies [243, 244] concluded that skeletal muscle function is sensitive to nutritional depletion and nutritional support. Humphreys *et al* (2002) concluded that hand grip strength predicted functional status in hospitalised patients. They were able to predict those patients who could not be discharged home and not able to perform their normal activities of daily living.

It could be considered that any intervention that can prevent decline or improve grip strength should have a significant impact on a patient's health and well-being.

1.3.4 Biochemical Assessment

The commonly used test to investigate suspected malnutrition is the measurement of serum proteins. Proteins that are commonly tested include; albumin, transferrin, thyroxine binding prealbumin and retinol binding protein, each having its own advantages and disadvantages. Albumin is probably the most commonly measured protein and is measured as part of routine clinical chemistry in hospitals [245].

Plasma protein synthesis is affected by malnutrition [246, 247] and two studies have shown that malnutrition was an important factor in the regulation of albumin synthesis [246, 248] [249]. However, other studies have not shown this, suggesting that chronic food deprivation does not result in hypoproteinaemia [250-254].

The reasons for the variation in studies is probably related to the multifactorial origin of hypoalbuminaemia [250-254]. Albumin has a half-life of 19 days and thus does not reflect short terms changes in protein status. Research has shown that although nutrition can contribute to changes in albumin concentrations, the most influential factor, is the metabolic response to stress [250, 251] infection [252, 253], burns [253], trauma and surgery [255, 256] all of which decrease plasma albumin. The reason for the decrease in serum proteins is mainly due to the increase in vascular permeability seen in catabolism, which occur in these clinical situations [254, 257, 258]. It is therefore inevitable that plasma albumin

levels will not increase in 'stressed' patients, until the inflammatory response has decreased [258].

The was reflected in a prospective study [259, 260] of 79 patients who underwent oesophagogastric surgery. Serum concentrations of interleukin-6 (IL-6), total protein, serum albumin, serum CRP, cortisol and other nutritional parameters were measured peri-operatively. All serum nutritional parameters decreased in the initial three days after resection, and improved, returning to preoperative levels within two-three weeks. This was with the exception of iron, transferrin and TIBC, which all returned to normal about one month after surgery. The authors attributed the drop in protein status to the acute phase response.

Oedema is a problem in surgical patients [255] as it deleteriously affects clinical outcome. Kinney (1986) [260] demonstrated that oedema appeared when the patient had gained 10% of body weight in extracellular fluid expansion. Starker *et al* (1985) [261] studied the administration of total parenteral nutrition (TPN) post-operatively and found that half of the patients gained weight. The authors attributed this to changes in fluid balance. The subsequent increase in fluid load reduced protein concentration [262], presumably via a dilution effect.

Despite these factors, all of which make interpreting serum protein levels difficult, serum protein, in particular albumin continues to be used as a nutritional marker. Based on clinical evidence, the use of albumin should be re-considered to be an indicator of illness and poor prognosis, rather than nutritional state [254, 263, 264].

A low serum albumin has been shown to predict complications and death post-operatively. Serum albumin concentration below 35g/l impairs the ability to withstand major illness, surgical intervention or a septic episode [240, 264, 265]. Gibbs *et al* (1999) [262] sought to evaluate the reliability of peri-operative albumin in predicting surgical outcome. They concluded that a drop in serum albumin from 46 to less than 21g/l was associated with an increase in mortality rates from less than 1-29% and in morbidity rates from 10-65%. Therefore, when looking at albumin concentration changes in sick patients, any improvement may indicate an improved clinical status rather than a corrected nutritional status.

Other proteins such as retinol binding protein, transferrin and pre-albumin have a shorter half life than albumin leading to the suggestion that they could be more sensitive indicators of nutritional depletion [256]. However, like albumin, they will also decrease in times of metabolic stress and can be affected by other factors discussed above [266] [259, 267].

1.3.5 Nitrogen Balance

Estimates of nitrogen balance provide information on whether a patient is in an anabolic or catabolic state [268]. Nitrogen balance is estimated by measuring the difference between the amount of nitrogen ingested and the amount of nitrogen excreted in urine, hair, sweat, faeces and skin as expressed in the following equation.

Nitrogen balance (g) = protein intake (g) / 6.25- urinary nitrogen (g) +4g losses.

Negative nitrogen balance in patients with surgical injuries, sepsis and other catabolic stresses reflects muscle protein catabolism. In clinical practice however, performance of nitrogen balance has limitations [269, 270] . In a study a positive nitrogen balance was reflected by a rise of pre-albumin in 88% of cases whereas a negative nitrogen balance was associated with a fall in pre-albumin in 70% of cases [271]. Nevertheless, it remains a useful measure in clinical practice [268].

1.3.6 Dietary Assessment

Malnourished patients often have or have had a reduced food intake. Often the treatment of malnutrition is to ensure that food or nutritional support intake meets the patients' requirements. An assessment of food intake is therefore important in not only identifying malnutrition, but also monitoring treatment.

Measurement of dietary intake is not a simple matter. For accuracy, techniques require a high degree of skill, care and dedication on behalf of the observer [272,

273]. There are a variety of methods for assessing dietary intake including 24 hour dietary recall and diet history which assess diet retrospectively, and dietary records, which may be either weighed or rely on estimated weights, to assess current intake.

A dietary history involves using a series of open and closed questions with regard to usual food intake. It should include questions on eating patterns and presence of symptoms that may affect food intake such as anorexia, nausea, vomiting, dysphagia, diarrhea, steatorrhoea, constipation, taste changes or increasing shortness of breath.

Studies conducted in an attempt to quantify the error in dietary assessment methods have found that most estimates using the 24-hour recall are accurate to ±10% [274, 275].

1.3.7 Nutritional Assessment Indexes

Because no single parameter has been found that will identify all patients at nutritional risk, investigators have developed indices in an attempt to improve accuracy. The five most common criterion assessments used for surgical patients are outlined in table 1.3.1. These criterions are mainly used in the research setting.

The best available method for nutritional assessment is a carefully performed history and physical examination [7, 276-278].

Table 1.3.1 Summary of Indexes

Index	Authors	Criteria Summary
Nutrition Risk Index (NRI)	Veterans Affairs (1991) [278]	NRI= (1.519x albumin, gl^{-1}) +(0.417 $\frac{\text{current weight}}{\text{usual weight}}$ X 100 NRI >97.5 borderline malnutrition NRI 83.5-97.5 mildly malnourished NRI <83.5 severely malnourished
Prognostic Nutritional Index (PNI)	Buzby and Mullen *et al* (1980) [7]	PNI (% risk)= 1.58-16.6(albumin gl^{-1})-0.78 (TSF, mm)-0.2 (transferrin, mg dl^{-1})-5.8 (delayed hypersensitivity graded 0-2. PNI<40% low risk PNI 40-50%intermediate risk PNI >50% high risk
Nutritional Index (NI)	Von Meyenfeldt *et al* (1992) [279]	NI= (0.14Xalbumin, gl^{1})+(0.03C%IBW)+(0.73XTLC 10^{9} l^{-1})-8.90. Values less than 1.31 are in indicative of malnutrition.
Subjective Global Assessment (SGA)	Detsky *et al* (1987) [225]	Five features: 1) Weight loss in 6 months 2) Dietary intake 3) Presence of GIT symptoms 4) Functional capacity 5) Metabolic demands
Maastrict Index (MI)	De Jong *et al* (1988) [280]	MI= 20.68-(0.24 X albumin, gl^{-1})-(19.21 pre-albumin gl^{-1})-(1.86 X TLC, 10^{9})$^{-1}$) –(0.04 X IBW) Patients with a score less than 0 are considered malnourished

(TSF Tricep Skinfold thickness; IBW Ideal body weight; TLC total lymphocyte count)

1.3.8 Summary of Section

There are many methods available for determining and monitoring nutritional status. This section has provided an overview of these techniques. However, the important message, is that no one assessment parameter, in isolation, will accurately determine if a patient is malnourished, or at risk of malnutrition. There are several methods that are particularly useful in the surgical patient; these include percentage weight loss, body mass index (BMI), mid upper muscle circumference and handdynanometry or hand-grip strength.

1.4 The Consequences of Malnutrition

1.4.0 Introduction

Starvation will lead to malnutrition and ultimately death. Malnutrition initially leads to an altered body composition, altered organ function and may therefore, have a significant effect on clinical outcomes. This section will explore this topic, outlining the generic consequences of starvation and describing how these effects influence surgical outcome.

1.4.1 Body Composition

Weight loss is the most prominent consequence of malnutrition. In cancer patients, weight loss is often the presenting symptom [176] with up to 66% of cancer patients reporting weight loss during the course of their disease [281]. It is reported that 45% of cancer patients have lost over 10% of their pre-illness weight at presentation [282].

Weight loss represents changes in body composition with all body stores, i.e. glucose, fat, fluid and protein stores being affected. Unlike glucose and fat, there is no inert protein store. Therefore, any depletion of body protein originates from lean body tissues, which will progressively impair organ function.

This alteration in physiological function is affected at certain percentage weight losses [236]. A summary of studies of percentage weight loss on physiological function is presented in table 1.4.1. It is apparent that as percentage weight loss increases, this is reflected by a negative affect on physiological function.

Table 1.4.1 The Physiological Effects at Key Percentage Weight Losses.

Author	Percentage weight loss	Physiological abnormality reported
Keys *et al* (1950) [236]	5%	General apathy
Studely (1936) [9]	10% weight loss	Reduced hand grip by 8-10% and subsequent reduced physical strength
Selzer *et al* (1982) Hill (1992), Peel (1997) [230, 283, 284]	10% weight loss	Increased post-operative complications
Winick (1994) [285]	18% weight loss	General physiological impairment
Russell *et al* (1983) [286]	20% weight loss	3-fold increase in mortality (23 % vs. 7%)
Sitges-Serra *et al* (1990) [287]	35% weight loss	45% reduced cardiac output, EEG abnormalities

In previously healthy individuals, starvation (water only) for 5 days resulted in a weight loss of 5% when compared to their usual weight [288]. Therefore, according to the work by Keys *et al* (1950) [236] it would appear that these individuals should report a degree of general apathy. A similar percentage weight loss was reported in a study by Brunn *et al* (1999) [289] comprising of surgical patients who remained nil by mouth with intravenous fluids. Eighty-three percent of patients reported weight loss and 33% of patients lost more than 5% of their admission weight. A similar study [290] demonstrated the average weight loss was 5% in 10 days in GI surgical patients who had standard management and no nutritional support. This was similar to the findings in oesophago-gastrectomy patients who received no post-operative nutritional support reported by Martin *et al* (1999) [170]. A post-operative weight loss was reported in 87% of cases; with 21% of patients losing more than 10% of their pre-operative weight.

Gianotti *et al* (2002) [291] examined patients undergoing elective surgery for carcinoma of the gastrointestinal tract. This study concluded that on average patients lost 4.8% of admission weight post-operatively. Thus, if the results of the studies presented in table 1.4.1 are considered, surgical patients who are kept have traditional management i.e. nil by mouth, must have deleterious physiological function.

The next section will present an overview of the evidence of the effect of malnutrition on muscle loss and organ function.

1.4.2 Organ Function

1.4.2.1 Cardiac Function

Cardiac function is grossly impaired in malnutrition [292-295]. Cardiac failure has been shown to be the possible cause of death in severe malnutrition [292-294].

The above studies reported that malnutrition leads to a reduced ventricular mass and results in reduced cardiac output, bradycardia and hypotension [296].

1.4.2.2 Respiratory Function

Malnutrition, resulting from reduced protein ingestion directly affects protein synthesis in the respiratory muscles [296]. Morphological changes in the lung and diaphragm are reported in patients with mild/moderate malnutrition [297]. Ventilatory drive is impaired in malnutrition [298]. The same authors showed that clinical semi-starvation for 10 days in healthy subjects reduced hypoxic drive by 42%, refeeding with nutritional support however, restored this response to normal.

The recruitment of macrophages into the lung and their subsequent activation is impaired in malnutrition. This has major impact on phagocytosis-a first line in pulmonary defense [296]. Cell mediated immunity is also impaired in the lung [299]. These effects have implications for surgical patients, particularly patients who have undergone thoracic surgery and abdominal surgery. A reduced cough pressure leads to increased susceptibility to chest infections. Malnourished patients often require ventilatory support for longer and are more difficult to wean from a ventilator [300].

1.4.2.3 Renal Function

The kidneys demonstrate little morphological or functional change in malnutrition [300]. In progressive starvation, the kidneys lose their ability to concentrate urine in the renal medulla, which lowers the renal medullary concentration gradient with subsequent polyuria.

1.4.2.4 Liver Function

Liver function and the number of hepatocytes are not impaired until near death in total starvation. The liver initially loses glycogen and subsequently gains fat. As starvation proceeds liver fat is utilised for energy and liver proteins are converted to glucose [300].

1.4.2.5 Pancreatic Function

The pancreas atrophies in starvation altering pancreatic exocrine and endocrine function early on in starvation and malnutrition [215].

1.4.2.6 Gastrointestinal Tract Function

The gastrointestinal tract (GIT) has many functions. It absorbs nutrients, is metabolically active secreting endocrine and exocrine products, and forms a microbiological barrier between the environment and the systemic circulation.

The effect of nutritional depletion on the GIT has been the subject of numerous studies. What seems apparent is that the presence of nutrients in the GIT lumen is essential for intestinal mucosal growth and function through the activation trophic GI hormones, the increase in intestinal blood flow and by the activation of the autonomic nervous system [301]. Malnutrition or nutritional depletion affects the GI in several ways:

1. Nutrient absorption

2. GI motility

3. Immunological impairment.

These factors will be discussed in the next section.

Nutrient Absorption

Nutrient digestion and absorption are affected in malnutrition [302]. Loss of weight is associated with altered mucosal architecture. Acute starvation, fasting and malnutrition alter villi height in humans [303], cause atrophy and thinning of the mucosa which all lead to a reduced surface area available for absorption. Coupled with this, there is a decreased brush border enzyme activity [304] further exacerbating steatorrhoea and diarrhoea, and hence increasing nutrient loss [305, 306]. A subsequent reduction in gastric acid production can cause bacterial overgrowth which further prevents the nutrients absorption at their receptors sites along the GIT.

Gut barrier function

In times of nutritional depletion or malnutrition, the gut barrier is thought to atrophy. This was the suggestion of trial of the affects of total starvation and very low calorie diets on intestinal permeability [307]. The authors established that starvation and malnutrition impaired GI permeability. They found an increased permeability to mannitol and lactulose after only short-term total starvation. The authors assumed that if increased permeability occurred to these molecules, then bacteria could follow the same route. However, a study in animals found that prolonged malnutrition did not lead to intestinal atrophy or bacterial translocation [308]. The same group did however find that bacterial translocation occurred in malnutrition only when the animals had developed an acute phase response (APR) [49]. Thus, malnutrition alone does not seem to cause translocation, but it does appear to render it more probable if it occurs in conjunction with a systemic insult. The effect of APR without malnutrition was not studied.

A subsequent human study demonstrated that malnutrition did increase intestinal permeability in the presence of an APR [309]. This was reported by another study [310] who also concluded that increased intestinal permeability positively correlated with circulating IL-6 levels. Both authors of these studies hypothesised that the GIT is the driving force behind the metabolic response to injury. This will be detailed in the following sections.

Gut Associated Lymphoid Tissue (GALT)

Recent evidence has linked malnutrition and the absence of enteral nutrition to impaired GALT function [311]. GALT comprises of immune cells located in the Peyers patches and mesenteric lymph nodes and cells within the intestinal mucosa. The impairment of GALT by the absence of enteral nutrition is the hypothetical reason why enteral nutrition has been demonstrated in some clinical trials to reduced infectious complications [49, 312-314]. This will be discussed in greater detail in section 1.5.

1.4.2.7 Immunological Function

Malnutrition profoundly affects immunocompetence, affecting all aspects of the immune system [315] but seems to have a particular impact on the cell mediated activity [316, 317]. Malnutrition is probably the commonest cause of secondary immunodeficiency world wide and is not restricted to developing countries [318]. It is apparent that malnutrition deleteriously affects all aspects of immunity.

Malnutrition leads to	Decreased lymphoid tissue
	Decreased lymphocytes numbers
	Decreased humoral immunity
	Decreased cell mediated immunity
	Decreased lymphocyte proliferation
	Decreased phagocyte function

Dowd *et al* (1984) [318]

Deterioration in immune function negatively affects the ability to recover from surgery. Two studies [319, 320] demonstrated that a suppressed immunity lead to more post-operative septic complications and increased mortality. Therefore it seems likely that if malnutrition leads to impaired immunity, then it must too lead to impaired surgical outcomes. This will be discussed later in this section.

1.4.3 Psychological Function

Starvation and reduced food intake have been shown to increase anxiety, depression and other behavioural changes. Studies by Leyton (1946) [321] of prisoners of war, reported that the first response to starvation and the reduction in food was the loss of sense of well being often long before the feeling of 'hunger'. The more prolonged the starvation the more progressive the mental and physical lethargy became [321]. The Minnesota study [236] detailed the effects of prolonged food restriction (24 weeks) on depression score. It was concluded that food restriction lead to social isolation and depression, having a major impact on the individual's quality of life.

In 1922, Sorokin working in Russia [322] concluded that,

"Starving individuals change ideals, convictions, beliefs, emotions and the whole outlook on life. Starvation mercilessly rips off the social garments and shows man as a naked animal."

The mechanism for this impaired psychosocial function is secondary to reduced protein synthesis as a result of reduced protein ingestion. These alter neurotransmitter production [323].

1.4.4 Health Related Quality of Life

A study [162] concluded that malnutrition led to significant impairment in health related quality of life (HRQoL). This study concluded that serum albumin, pre-albumin and a weight loss of greater than 10% predicted a patient's perception of life satisfaction.

A study by Ferguson and Capra (1998) [324] reviewed 456 admissions to a hospital in Australia and concluded that the patients with malnutrition reported reduced quality of life scores when compared to well nourished patients ($p< 0.05$). This study used The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

Hammerlid *et al* (1998) [325] also looked at HRQoL and malnutrition in a group of patients with head and neck cancer. They found that malnutrition did not correlate with HRQoL. Following major surgery it is reported that patients experience a pronounced feeling of fatigue for one month. This fatigue correlates with nutritional status, and impaired muscle strength. One study in community patients post discharge who had undergone major surgery reported that 10% of patients who were well-nourished had become malnourished within 6 weeks of surgery [326, 327].

1.4.5 Wound Healing

Malnutrition and recent nutritional intake are key factors in the complex mechanism of wound healing [328]. Malnutrition has been linked to impaired wound healing in surgical patients [3, 328, 329]. Even acute starvation for a few days is detrimental to wound healing [330]. Goodson *et al* [331] showed that even a 1-2 day inadequate nutrient intake decreased hydroxyproline synthesis one of the main components of collagen.

Haydock and Hill (1987) [332] studied 36 surgical patients, divided on the basis of their pre-operative nutritional status to 'normally nourished',' mildly malnourished' and 'moderately malnourished'. They found that wound strength

was half the normal strength in patients who were even mildly malnourished. Pre-operative oral food intake is also important in wound healing as demonstrated by Windsor (1988) [333]. The authors' found a positive correlation between pre-operative nutritional intake and improved post-operative wound healing. This is relevant, as in clinical practice it is not uncommon for patients in the week prior to surgical intervention to have numerous radiological interventions and hence prolonged periods of 'nil by mouth'.

Few studies have looked specifically at anastomotic strength in surgical patients. A study of rats [334], concluded that hypoproteinaemia and weight loss correlated with the bursting strength of anastomosis. In patients with a low serum albumin there was an increased tendency for suture dehiscence [335]. However, albumin does not reflect nutritional status *per se*, but may reflect the inflammatory response, which as discussed may be influenced by nutritional status.

1.4.6 Malnutrition and Surgical Risk

Studely [9] described the effect of malnutrition on surgical outcomes in 1936. He concluded that malnutrition negatively impacts on surgical outcomes. Since this work, the clinical management of surgical patients has progressed, with the availability of prophylactic antibiotics, intravenous fluids and colloids, increased understanding of the use of anaesthetics and analgesics, specialist critical care units and an increased understanding of organ function peri-operatively.

However, the use of nutritional intervention in optimising surgical outcome remains controversial. Several prospective studies have indicated that patients undergoing surgery are at nutritional risk and this can have a deleterious effect on clinical outcome. A review of the studies is presented in the following section.

1.4.6.1 Retrospective Studies

A study by Windsor (1988) [5] concluded that a pre-operative weight loss greater than 10% created a marked negative effect on liver, skeletal muscle, respiratory muscle and psychological function. These patients also developed more post-operative complications when compared to patients without weight loss. In addition, the author suggested that the presence of hypoalbuminaemia might exacerbate further septic complications including pneumonia causing an increased time in hospital for patients.

Similar findings were demonstrated with a 20% weight loss. These patients had a three times more higher risk of dying then those who had no weight loss (23% versus 7%) [10]. Conti *et al* (1977) [11] demonstrated a higher morbidity and mortality rate in patients undergoing oesophago-gastrectomy with a weight loss greater than 15% compared to those with less than 15%. Once again sepsis was the main cause of morbidity and mortality in this study. The authors hypothesise that this may be related to the effect of malnutrition on the immune status of the patient and therefore may have an impact on the frequency of complications.

A study by Meijerink *et al* (1992) [336], analysed the additional risk to surgical patients undergoing major GI surgery caused by suboptimal nutritional status. Well-accepted surgical risk factors such as age, co-morbidities, type and extent of surgical procedure, skill of the surgeon and the disease itself, were all significantly correlated with surgical outcome. Following multivariate regression analysis the severity of malnutrition was positively associated with the severity of the complication.

A summary of the cohort studies of the effect of malnutrition on surgical complications, clinical outcome and hospital mortality are presented in table 1.4.2. All of the 6 studies [5, 7, 170, 337, 338] indicate that a weight loss of greater than 10% peri-operatively leads to more complications. Two studies link a weight loss greater than 10% to increase risk of death in major surgical patients [327] [338].

Table 1.4.2 Summary of the cohort studies of the effect of malnutrition on surgical complications, clinical outcome and hospital mortality

Authors	Surgical studies	Nutritional status pre-operatively	Increase in complications	Increased LOHS	Increased mortality
Corish *et al* (1998) [327]	Major cancer surgery	Weight loss >10% in 6 months	Yes	Not reported	Nor reported
Braga *et al* (1995) [337]	GI cancer surgery	Weight loss >10% in 6 months	Yes	Yes	Not reported
Martin *et al* (1999) [170]	Cancer surgery	Pre-op weight loss>12%	Yes	Not reported	Not reported
Buzby *et al* (1980) [7]	Major Surgery	PNI >50	Yes	Yes	Not reported
Windsor *et al* (1988) [5]	Major GI surgery (mixed)	Weight loss>10%	Yes	Yes	Not reported
Bozetti *et al* (2001) [338]	UGI cancer surgery	PNI >50	Yes	Yes	Yes

1.4.7 The Economic Impact of Malnutrition

This section has so far reviewed the effects of malnutrition on physiological, psychological and social function. This next section will present a summary of the evidence on the effect of malnutrition on the cost of healthcare.

A study by Allison *et al* (1992) [339] concluded that patients with unintentional weight loss greater than 10% of their usual body weight have more complications, higher mortality, longer hospital stays and therefore use more healthcare resources than well nourished individuals. In the USA, individuals whose BMI falls outside the normal range have greater health care expenditure. In 1993, a calculation was made suggesting that healthcare expenditure increased progressively as BMI decreased, from $1850 for a woman with a BMI of 21 kg m^2 to $2350 for a woman with a BMI 15 kg m^2. In men the figure was more pronounced with BMI 21 kgm^2 equating to $1300 and $3250 for a BMI of 15 kg m^2 [340].

The recently published NICE guidelines (2006) suggest that malnutrition costs the NHS £7.3 billion in actual expenditure per annum [341].

Other studies have shown that malnourished patients have higher hospital costs when compared to well-nourished patients [342] [343]. Robinson *et al* (1988) [342] concluded that malnourished patients had increased hospital costs $7,692 per patient -compared to $5,142 for well-nourished patients.

Reilly *et al* (1988) [343] also concluded that malnutrition increased hospital costs. They found that the costs of treating infections in patients undergoing surgery for cancer increased costs by $12,542 per patient and more infections occurred in patients who were malnourished.

Other work has demonstrated that the duration post-operatively without adequate nutritional intake correlated with increased length of hospital stay [344].

The same study [344] verified that malnourished patients had increased length of hospital stay when compared to well-nourished patients (23.5 days versus 16.5 days $p<0.01$). Thus malnourished patients had a prolonged hospital stay by 50%.

To date, few studies have looked at the impact of malnutrition after discharge from hospital after surgical procedures. Linn *et al* (1984) [345] reported more infectious complications in the year post discharge if the patients were malnourished at the time of discharge after being hospitalised for surgical intervention. Another study, Friedmann *et al* (1997) [346], reported a higher risk of non-elective readmissions post discharge in patients with malnutrition at the time of discharge.

1.4.8 Summary of Section

This section has provided an overview of the effects of malnutrition on both physiological and psychological function. The effects of malnutrition on the gastrointestinal tract, immune and muscle function are important as these have an impact on the development of complications in terms of morbidity and mortality. Impaired wound healing and complications all lead to increase in LOHS and increased health care costs.

Malnutrition instigates a range of physiological and clinically relevant effects ranging from impaired organ function to increase mortality. Malnutrition can also increase hospital expenditure.

These effects all need to be taken into account in the design of clinical trial of nutritional support to determine functional, clinical and financial outcome indicators.

1.5 Nutritional Support

1.5.0 Introduction

The first documented use of nutrition intervention in the treatment of sick patients dates back to the Ancient Egyptians. Wine, whey, milk and barley enemas were administered in an attempt to improve recovery [347].

In the late 18th century, John Hunter gave the earliest recorded enteral nutritional support, to a dysphagic patient after a stroke. The enteral feeding tube was made from a whale bone and eel skin and the 'feed' was squeezed into the stomach by a reservoir made out of pig bladder [347].

In the 19th century, it was common practice to withhold food or fluid in the febrile or ill patient. However, in the late 1890s after the discovery that a fever increased the metabolic rate by 40%, it was deemed important to 'feed a fever' [348].

In 1932, Sir David Cuthbertson [206] studied the effects of trauma and injury on protein homeostasis. He concluded that ill or injured patients were 'catabolic' with resulting progressive degradation of lean body mass. This was characterised by increased urinary nitrogen, proportionate to the severity of the injury. These studies formed the basis of the understanding of the relationship between surgical injury and the development of protein depletion.

In 1936, the relationship between surgical outcome and nutritional status was demonstrated by Studely [9]. He concluded that pre-operative percentage weight loss correlated with increased risk of death post-operatively. Other factors such as age, impaired cardiac and respiratory function, type of surgery, duration of surgical procedure and the surgeon performing the operation were not associated with changes to clinical outcome. He attributed this deleterious outcome to the impaired immune function which is typical in malnourished patients. He concluded that more patients could be saved, provided efforts are concentrated on the pre-operative preparation of those who have lost a great deal of weight [155].

Some years later, Cannon (1944) [349] demonstrated that reduced protein intake peri-operatively increased the incidence of post-operative infections. It was at

this time that early case studies highlighted the feasibility of enteral nutrition post-operatively [350, 351]. Patients who received enteral nutrition had increased energy and protein intakes (3050-4700 calories and 17.7-28 grams nitrogen per day), reduced weight loss; maintenance of plasma proteins and preservation of lean body mass characterised by a reduced loss of urinary nitrogen as opposed to patients who remained nil by mouth [350, 351].

Dudrick *et al* (1968) [352] subsequently defined the method of delivering Total Parenteral Nutrition (TPN) demonstrating that puppies could be solely 'nourished' by its use in the late 1960s. Efforts by Wretlind (1972) [353] led to the rapid gain in popularity of TPN in surgical patients. Subsequently, the use of TPN has been used often without criticism as the optimum way of delivering nutrition to surgical patients. Little attention was made to EN in surgical patients until the last 5-10 years when theoretical benefits of EN over TPN were suggested.

Over the last 40 years, numerous clinical nutrition trials in surgical patients have been conducted. These trials have often used functional endpoints; such as weight loss, muscle loss, reduced muscle strength, poor immunological status and impaired wound healing. These are deemed important as inadequacies in these may manifest in the development of complications, impairing clinical outcome. Thus, improvements in these functional or surrogate endpoints are often extrapolated to provide a prediction of clinical outcome.

The most common and best-studied method of treating malnutrition is the use of nutritional support; either oral supplements, liquid enteral feeds or parenteral nutrition [341]. Nutritional support provides macro and micronutrients. Other methods include fortifying foods so that meals are more nutrient dense. However, this method is not useful in patients who are unable to eat, such as after major GIT surgery.

This following section will firstly present the clinical trials of nutritional support which used surrogate and functional endpoints. It will then examine the evidence

for the affect of nutritional support on clinical outcome in patients undergoing major surgery. It will scrutinise the use of both parenteral and enteral nutritional support, and how these impact on clinical outcome.

1.5.1 Nutritional Support: Impact on Nutritional Outcome

Functional or surrogates outcome markers have often been reported in clinical nutrition trials. These indicators are usually extrapolated to suggest either a benefit or detriment of nutritional support in patients.

The trials in this section are classified into the effect of nutritional support on:

1. Body weight,

2. Nutritional intake,

3. Body composition

4.Body functions, namely wound healing, immune function and gastrointestinal function.

1.5.1.1 Nutritional Support and Weight Loss

Ten studies have looked at the effect of nutritional support on weight loss, in patients undergoing major GIT surgery [13-16, 18, 354-358], three of these studies [354-356] have demonstrated that TPN post-operatively reduced weight loss. The other studies [15, 16, 357, 358] with the exception of one by Watters *et al* (1997) [14] concluded that enteral nutrition (EN) via a feeding jejunostomy attenuated weight loss in post-operative GI surgical patients when compared to patients who received standard management i.e. nil by mouth and intravenous fluids.

Three trials have shown that EN was superior to maintain weight when compared to STD management. An RCT [15] showed no mean weight loss in the EN group (mean calories =1138/day for 5 days) versus a weight loss of 2kg (range 5.8kg loss to 0.5kg weight gain) in the standard management group.

Hoover *et al* (1980) [357] concluded that in a population of 49 patients following UGI surgery, weight loss was lower in the EN group (0.02 kg after 10 days of 1350 calories/day) as compared to the standard group (3 kg loss, nil by mouth until allowed to eat and drink.)

Ryan (1981) [18] showed that patients who received 1430 calories per day from EN compared with nil by mouth for 6.6 days lost less weight (3.7 kg) than controls (5.6 kg) for the first post-operative week. Interestingly none of the studies reported calorie intakes that exceeded 1400kcals/day.

One study by Muggia-Sullam *et al* (1985) [359] compared the efficacy of TPN and EN in maintaining body weight. The authors demonstrated that both modalities were equivalent in promoting nitrogen balance, preserving weight and promoting protein synthesis.

None of these trials addressed the issue of fluid balance and development of oedema as contributory factors for weight changes in surgical patients.

1.5.1.2 Nutritional Support and Nutritional Intake

Six studies [12, 16, 18, 357, 360, 361] have reported that EN increased nutritional intake in GIT patients post-operatively. This is not surprising as the control group remained 'nil by mouth' and hence had no nutritional intake until initiation of oral intake.

Enteral tube feeding bypasses both the cephalic and oral stages of digestion; therefore it is possible that disturbances in appetite sensations may occur. Subsequently, it is assumed that the use of nutritional support will delay or suppress a patient's ability to resume oral food intake post-operatively, however this not supported by the findings of several RCTs [15, 18, 357, 361]. These studies concluded that food intake was similar (if not greater) for the patients who received EN as compared to STD management (nil by mouth). In an elegantly designed study, Bastow *et al* (1985) [362], the authors observed that overnight nasogastric feeding in patients with fractured neck of femur, was associated with a doubling of voluntary oral intake.

The mechanism for this increase in oral food intake may be related to a modifying effect of EN on the inflammatory response [363]. However, studies in rats of TPN [364] and intragastric feeding [365] indicate that the continuous infusion of nutrients decreased spontaneous food intake, the decrease in food intake being proportional to the density and duration of nutrients infused. After cessation of either TPN or EN, food intake normalised within 3 days. The possible mechanism may centre on receptors in the portal vein that may detect the concentration of nutrients in the portal circulation, signaling via the vagus nerve to the hypothalamus. Increase nutrient concentration activates the efferent loop inducing a satiated feeling, hence reducing food intake, stimulating gastrointestinal motility and gastric emptying [366, 367].

1.5.2 Nutritional Support and Physiological Function

1.5.2.1 Nutritional Support and Muscle mass and Strength

As discussed, a reduction in muscle mass and strength in surgical patients deleteriously affects the function of skeletal, cardiac and respiratory muscle.

Several studies have concluded that nutritional support post-operatively attenuates muscle and fat loss in surgical patients [13, 14, 16, 361, 368].

Carr *et al* (1996) [13] reported that surgical patients who received early EN for the first seven days post-operatively lost less muscle strength (using handdynanometry (HD)) compared to 'nil by mouth' and intravenous fluids (6.7kg weight gain versus 9.6 kg weight loss in the EN and control group respectively.)

However, this was not the finding of Watters *et al* (1997) [14], who reported no differences in muscle strength (using HD) in patients who received EN versus 'nil by mouth' in the first seven days post-operatively after major UGI surgery. The same RCT reported that post-operative vital capacity and forced expiratory volume in 1 (FEV1) was consistently lower in the EN group as compared to controls [14]. This impairment may have been related to the high incidence of abdominal distension (62%) that was attributed to the 'aggressive' enteral feed

regimen (2500mls/day EN delivered by the second postoperative morning) used in the EN group.

Also, the majority of the STD group received their pain relief from epidurals compared to the EN group who received systemic opioids that are associated with altered GI motility [369]. This may also have been a contributory factor in the abdominal distension in the EN group.

1.5.2.2 Nutritional Support and Immunological Function

Patients who become anergic after surgery have a very high death rate, mainly due to infectious complications [319]. Nutritional support is thought to have a direct positive affect on immunological function. However, the impact of nutritional support on immunological function is not straightforward. Most studies have assumed that a reduction in infections reflects enhanced immune function rather than studying the affect of nutritional support on the immune system *per se*.

One study, did however conclude that TPN corrected anergy in malnourished cancer patients [370]. This was not the conclusions of a study by Beier-Holgerson *et al* [12], who investigated the effect of EEN versus placebo on cell-mediated immunity (CMI). Sixty patients were studied; patients were stratified for preoperative nutritional status. CMI tests were applied 2 days before surgery and days 1 and 5 postoperatively; the authors concluded there were no significant differences in CMI scores between the groups, likewise nutritional status did not appear to influence CMI.

More recently, RCTs have studied the role of immuno-nutrition in improving immunity. Cerra *et al* (1991) [371] conducted a randomised blinded prospective trial comparing two nutritionally complete enteral nutrition formulas, (one supplemented with arginine, menhaden oil, and RNA) on anergy and suppression of immune function in critical care patients. After 7-10 days of enteral nutrition in patients with persistent sepsis, both EN formulas achieved improved nitrogen balance and improved visceral proteins, yet there was no improvement in anergy [371].

The effect of EN on the development of infections (in particular respiratory infections) has been reported by Kudsk *et al* (1996)[312]. This RCT compared enteral and parenteral nutrition and demonstrated that enteral nutrition reduced infection rates from 31% in TPN to 11% with enteral nutrition. There was no STD management group, however.

Human studies have concluded that patients who did not have EN had more MOFs [313], a less favourable prognosis [372] and have increased rates of septicaemia, in particular which stem from bacteria derived from the intestines [49, 314].

1.5.2.3 Nutritional Support and the Acute Phase Response

Similarly, EN is thought to modify the acute phase inflammatory response (APR) [373-375]. Studies have illustrated that following initiation of EN, C-reactive protein synthesis is reduced with a subsequent improved liver synthesis of albumin and transferrin. These studies [374, 375] have suggested that EN modulates the acute-phase response while reprioritising visceral protein synthesis. Interestingly, a study by Kudsk *et al* (1998) [376] concluded that the patients most likely to benefit from EN were the most metabolically unstable patients with the highest APR.

The role of EN in attenuating the APR, was reflected in another study [377] of surgical patients. The authors concluded that nutritional support prevented early nitrogen loss after GI surgery, suggesting that EN reduces catabolism. Similar findings were reported in two further RCTS [378] [379]. Hochwald *et al* (1997) [378] randomised patients to either EEN or STD post-operative management (IV fluids), with the aim of determining whether EEN improves visceral proteins in postoperative upper GI cancer patients. The randomised groups were comparable at baseline for diagnosis, procedures, serum albumin and preoperative weight loss (n=29). The study concluded that EEN improved nitrogen balance ($p<0.001$). The authors suggested that reduction in catabolism of proteins, muscle and fat mass maybe secondary to an increased production of

insulin (an approximate two-fold increase in insulin), which is an anabolic hormone. Singh *et al* (1998) [360] supported these findings. They concluded that patients who received EEN within 24 hours post-operatively were in a positive nitrogen balance on day 3 whereas the controls (nil by mouth) remained in a negative nitrogen balance for 10 days. Both these studies, give a possible insight into the mechanisms why enteral nutrition may contribute to a reduction in postoperative morbidity and mortality.

1.5.2.4 Nutritional Support and Wound Healing

The studies of the role of nutritional support in wound healing in surgical patients are limited. Animal studies (rats) have shown that the use of EEN had a significant effect on wound collagen accumulation and therefore a higher wound tensile strength, in the earlier phase of healing as compared to PN [380].

Clinical trials from the 1980s, highlighted that malnourished patients (N=470) who received PN for 1 week post-operatively had improved collagen synthesis and wound healing when compared to standard management [332].

Similar findings were reported by Schroeder *et al* (1991) [16]. The authors in this study used EN in patients after GI resection, and compared it to 'nil by mouth' and IV fluids. EN was continued until the patients were able to eat and drink normally. The results indicate improved collagen synthesis, stronger wound strength in the EN group. However, a small RCT by Sagar *et al* (1979) [15] refuted this. They concluded that EN versus STD management who compared enteral tube feeding and standard management and did not improve wound healing.

The role of EN post surgery in anastomotic healing has been studied more recently. A meta-analysis by Lewis *et al* (2001) [17] of 11 RCTs demonstrated that anastomotic dehiscence rates were reduced in patients receiving EN. This is consistent with the study by Braga *et al* (2001) [381] which reported an improvement in anastomotic healing in patients receiving EEN.

A study by Khalili *et al* (2001) [382] concluded that early post-operative EN increased intestinal anastomotic strength, even in the presence of sepsis. Enteral nutrition also reduced TNF-alpha, which corresponded with an improvement in healing of the anastomosis [382]. Despite these being relatively small studies the role of EN in anastomotic healing looks favourable.

A study by Braga *et al* (2001) [381] also suggested that EEN was not detrimental for anastomotic healing even when an early direct passage of nutrients over a fresh intestinal suture has occurred. They studied 270 gastrectomised patients and did not observe any jejunal ileal anastomotic leaks even though patients were fed proximally to this via a nasojejunal enteral tube.

1.5.2.5 Nutritional Support and Gastrointestinal Tract

The role of nutritional support in the optimal function of the GIT has been a key area of research over the past few decades. This section will present a review of the evidence to date. It will focus on the effect of nutritional support in the two main areas of controversy, namely GIT motility and GIT barrier function. A review of normal GIT motility is presented in appendix I.I.

Gastrointestinal Motility

After GI surgery, postoperative gastrointestinal dysfunction (PGID) or ileus is common, occurring in 90% of patients [383].

Livingston and Passaro (1990) [384] described ileus as,

> *"The inhibition of propulsive bowel motility, irrespective of pathological mechanisms"*

Ileus is characterised by the development of nausea, vomiting, delayed gastric emptying, bowel distension, decreased bowel sounds, delay in passage of stools and pain after a surgical procedure [385] [386]. Studies report that ileus increases patient suffering and increases the tendency for more complications, prolonging hospital stay [383, 387, 388]. The economic impact of ileus has been estimated to be $750 million to $1 billion in the United States in 1999 [389].

The pathogenesis of ileus is multifactorial, the origin is thought to stem from the high concentration of inflammatory mediators following any injury to the intestinal muscularis of the GI tract. The cytokine cascade has been demonstrated by several studies [390-392]. Intestinal surgery activates the macrophage network in

the intestinal luminal wall setting up an inflammatory reaction. These macrophages express CD11A and CD11b and CD18 and interleukins IL-1, IL-6 and TNF alpha. These act locally to initiate morphological changes in the bowel wall. In addition, these immunological cells cause an increase in free radical production, disrupting the membrane ion-channels (potassium and calcium) that regulate smooth muscle contraction and rhythm. This results in a decrease in circular muscle contraction and a reduced intestinal transit time. Subsequently, systemic cytokines, prostaglandins and catecholamines are released which activate the autonomic nervous system. This produces the inhibitory effects of altered motility and reduced mesenteric blood flow [384, 393, 394].

Interestingly, the length of the surgical abdominal incision has not been shown to correlate with return of normal GIT function post-operatively [395]. Neither the extent nor the duration of the operation appeared to correlate with the severity and duration of ileus [396]

Many other factors affect PGID:

1. Neuropeptides in particular substance P and endogenous opioids are released in response to the pain of surgery and have been linked to post-operative ileus [397]. Opioids have a direct affect on gastric emptying and intestinal small muscle contractile activity [369]. The mechanism is complex. Opioids initially stimulate the Migrating Motor Complex (MMC) to increase contractile activity in the small bowel however; however, this is then followed by a prolonged period of atony leading to a reduced transit time. Likewise, it has an inhibitory effect on colonic motility [369].

2. The avoidance of general anaesthesia and analgesia is associated with a reduced incidence of PGID. A study has shown that epidural analgesia reduces PGID compared to opioids anaesthesia [398]

3. Post-operative fluid balance affects GI motility. A positive fluid balance leads to interstitial oedema, which can lead to GIT oedema [255]. Lobo *et al* (2002)

[399] concluded that fluid and sodium restriction in patients undergoing major colonic resection significantly reduced the duration of PGID. Maintaining optimal fluid status was shown to improve GIT perfusion and reduce PGID [400]. However, this was not the findings of a further study by Cook (1989) [401], which found that regulating fluid regimens did not have any effect on post-operative ileus.

4. Disturbances in acid-base balance, glucose or electrolytes affect PGID. Hypokalaemia, hyponatraemia, low serum magnesium levels and acidosis all cause delayed gastric emptying and ileus [402] presumably due to the direct alteration in cellular mechanics. One study attributed even relatively mild hyperglycemia and hypoglycemia to altered GIT motility [403].

5. There are many other factors, which have been linked to ileus such as nitric oxide, reserpine, calcitonin, nasogastric intubation, gum chewing, using laproscopic procedures, pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDS), prokinetics such as metaclopramide hydrochloride, erythromycin (a motilin receptor antagonist), cisapride (a serotonin antagonist), ceruletide (a peptide that may enhance intestinal motility) and octreotide a somatostatin analogues that inhibit the secretion of gastrointestinal hormones. These are all reviewed extensively by Mythen (2005) [383].

Enteral Nutrition and Its Effects on Gastrointestinal Motility

In surgical patients, it is thought that PGID prevents the safe delivery of EN. Barium studies demonstrated that small bowel motility continues in the post-operative phase, with delayed gastric emptying, taking 24 to 48 hours to recover and colonic motility taking 3 to 5 days to return [384].

Some clinicians continue to use the traditional practice of auscultation of bowel sounds to gain information on intestinal function and motility. However, bowels sounds have not been shown to correlate with motor patterns of function or dysfunction [404-414]. To date, there are few non-invasive techniques available

to quantify gastrointestinal motility. This is an important area of research, as the ability to determine adequate GI motility would undoubtedly prevent patients suffering from a prolonged period 'nil by mouth'.

The administration of EN has been shown to promote bowel function in three studies of post-operative surgical patients [12, 68, 415]. However, this was not seen in two RCTs, both of which concluded that EN did not alter bowel function post-operatively [16, 416] .

To understand why these studies produced differing outcomes an understanding of normal GIT motility is essential (appendix I.I). Normal GI motility occurs in two states; fed state and fasting state [417].

The fed state. The efficient absorption of nutrients from chyme in the upper small intestine is dependent on repeated segmental peristaltic waves. These waves ensure the mucosa 'dips' into the chyme, promoting optimal absorption. At the same time, the villous contractions increase both blood and lymphatic flow to enhance the uptake of nutrients, resulting from digestion and absorption [418].

The fasting state. In the fasting state, small intestinal motility is characterised by periods of inactivity and activity. The migrating motor complex (MMC) occurs 4-6 hours after ingestion of nutrients. It is characterised by 4 phases [419].

1. Phase I- a phase of inactivity

2. Phase II-a period of irregular spike activity lasting for 30-40 minutes. Pressure activity increases during phase II

3. Phase III- intense contraction

4. Phase IV- pulsating waves of contraction

The whole cycle of activity migrates down the upper small intestines at 4-6 minutes intervals. MMCs normally occur only in the fasting state and have the

function of sweeping food and bacteria debris down the small intestine. MMCs typically do not occur until 4-6 hours after a meal [420].

The route, rate and concentration of nutrients delivered into the GIT produce differing GI motility affects. Studies of gastric feeding delivered at a constant rate caused continuous gastric emptying. The rate of the gastric emptying was proportional to the EN infusion rate, caloric load and the osmolarity of the feed. However, when the feed rate exceeded 3kcals/minute, gastric emptying was impaired [421], increasing the risk of vomiting.

The effect of intragastric feeding on small intestinal motility was demonstrated in a study of healthy volunteers. Polymeric enteral feed was delivered continuously into the stomach via a nasogastric tube, at concentrations of 1 kcal per minute and 1.38 kcals per minute. Neither rate of the feed elicited the normal fed state motility response [214]. Propagating Migrating Motor Complexes (MMCs) were seen throughout both the infusions of the intragastric feed [422].

In contrast, when the feed was delivered into the duodenum a fed state motility pattern occurred, with abolition of the MMCs [214]. There was also an increase in colonic motility, with the increased nutrient delivery per minute [423]. Thus, post-pyloric EN appears to be superior to gastric feeding in stimulating GIT motility.

One study [424], did however demonstrate that delayed gastric emptying occurred in patients who underwent pylorus-preserving pancreaticoduodenectomy (PPPD). All patients received a continuous jejunal infusion of EN. The reason for this could stem from the actual surgical procedure or could be attributed to the presence of high concentration of nutrients in the small bowel initiating an endocrine feedback mechanism, preventing further nutrients being decanted into the small bowel.

This section has provided evidence to suggest that when EN is delivered in clinical practice, the delivery of the EN should not be perceived as simplistic. Attention to the delivery of the EN, in particular to the feed rate, is important, as

failure to increase the feed rate may not produce a post-prandial motility response. This will result in the prevention of a normal small bowel contraction and peristalses, resulting in undigested EN passing into the colon [417].

Gut Barrier Function

The primary role of the GIT mucosa is to act as a defense barrier, preventing bacteria and endotoxins from entering the systemic circulation. The small bowel has a constant exposure to multiple pathogens and so contains an extensive immunological system [425]. The 'normal' intestinal mucosa is lined with tight junctions between the mucosa cells, which prevent the movement of pathogens into the portal circulation via the paracellular channels [426]. In addition, a multitude of immunological cells are present in the intestinal wall.

It is hypothesised that during periods of 'stress', following the activation of a APR, disruption of the gut barrier function occurs [427-431]. Bacteria which are normally resident in the lumen of the intestines barrier, are able to migrate and act as sources of sepsis at distant sites [432, 433] .

One published clinical trial studied GIT morphology and bacterial translocation in surgical patients [434]. The authors collected ileal serosal biopsies and an ileal mesenteric lymph node biopsy for culture, at the start of surgery. They concluded that translocation occurred in 10.3% of patients.

In section 1.4.2.5, the effect of malnutrition on GIT structure and function was discussed. Surgical patients traditionally have a period of 'nil by mouth' resulting in 'bowel rest'. This bowel rest has been correlated with a reduction in mucosal mass of 50% and mucosal atrophy, occurring within days [435].

Similarly, failure to supply enteral nutrients as occurs with the use of TPN, caused a reduction in mucosal thickness, reduces villous height, increases gastrointestinal tract (GIT) oedema, reduces GIT permeability, alters GIT barrier function and leads to GIT mucosal atrophy with the subsequent increased bacterial translocation of luminal bacteria into the systemic circulation [48-51].

Sedman *et al* (1994) [434] concluded there was, however, no correlation between 10 days of preoperative TPN and nutritional status and intestinal villous height and translocation in patients undergoing open laparotomy. Septic complications were twice as high in patients with bacterial translocation but the organisms causing the infection did not originate from the GIT lumen.

Similar mucosal changes as seen with TPN have been shown to occur with elemental enteral diets [436, 437]. Elemental enteral feed caused mucosal atrophy, decrease digestive and absorptive products which are important in the regeneration of GIT mucosal structure and GIT function [438]. Interestingly, whole protein enteral nutrition was considered superior to TPN and elemental diets, in maintaining GIT function and integrity. This was first published by Kudsk (1981) in laboratory studies [41] and Alexander (1980) in clinical studies [42]. These studies supported previous rat studies, which suggested that GIT mucosal atrophy occurs in the absence of enteral feeding [43, 44]. Enteral nutrition is thought to have a trophic effect on GIT structure and integrity, contributing to the maintenance of GIT barrier function and protecting against invasion by bacteria and toxins, with one study by Maxton *et al* (1989) [45] demonstrated no deterioration in GIT morphology post-operatively in surgical patients who received EN. This was however refuted in a study by Cummins *et al* (1995) [439]. This study demonstrated that there was no benefit of EN in preserving GIT morphology. This study did not however report when the delivery of EN was commenced after the operation. This is crucial as it is possible that EN is less effective after hypermetabolism has been initiated.

This crucial 'window' when EN delivery seems optimal was supported by an animal study by Mochizuki *et al* (1984)[427]. The authors concluded that if EN was commenced immediately, within 12 hours, after an injury, preservation of the GIT mucosal structure and attenuated the catabolic response occurred. If EN was delayed for 72 hours the animals developed a hypermetabolic state (characterised by increased stress hormone concentrations and increased oxygen consumption). All animals, in the delayed EN group, developed mucosal atrophy. The authors hypothesised that the hypermetabolic state may have

originated from the intestines, caused by pathogens entering the systemic circulation by bacterial translocation.

It is apparent from the above that studying the role of nutrition, 'nil by mouth' or malnutrition on translocation in human studies is challenging. There are few published clinical trials. Several RCTs [440-442] have not demonstrated that EN was superior to TPN in maintaining GIT integrity and hence reducing GIT permeability. Brooks *et al* (1999) [440] examined patients (N=26) after resection of upper GI cancer and compared EN via a needle catheter jejunostomy (NCJ) with standard care (nil by mouth with IV fluids) and concluded that GIT permeability increased in all study patients post-operatively returning to normal day 5 postoperatively. All patients were well nourished preoperatively.

A RCT (N=67) compared the effect of EN and PN on GIT permeability [441] in patients undergoing major upper GI surgery. Patients were randomised prospectively to receive either seven days postoperative EN (n=33) or TPN (n=34). The groups were matched for age, sex, nutritional status, surgical procedure and blood transfusions. The mean energy and nitrogen intake over the seven days was not significantly different between the two groups. The results show no significant difference in the incidence of non-infective complications or the number of total infection episodes between the two groups. EN once again did not significantly modulate GIT permeability determined by the lactose/mannitol test. Intestinal permeability was increased after surgery but returned to normal by day seven in both groups. Kompan *et al* (1999) [442] showed no benefit of EN over PN in altering post-operative GI permeability in critical care surgical patients.

Alternatively, one RCT [13] demonstrated that EN as compared to TPN led to a significant reduction in GIT permeability and hence possibly improved GIT integrity in patients undergoing intestinal resection ($p<0.05$). There was a corresponding reduction in the development of infective complications. This trial has a small sample size but does infer that EN may 'protect' GIT morphology and maintain GIT integrity, preventing the translocation of pathogens, hence the

reduced number of infective complications. The exact mechanism is only speculative, as the trial did not isolate systemic pathogens and mesenteric lymph node pathogens, which would have provided an insight into the mechanism of translocation. To date, there appears to be no consensus as to whether EN is superior to TPN in maintaining GIT barrier function as reported in two review papers [443, 444].

1.5.3 Nutritional Support and Health Related Quality of Life

As indicated in section 1.4.4 malnutrition impacts on health related quality of life (HRQoL). The World Health Organisation defines HRQoL as:

> *'An individual's perception of his or her position in life in the context of the culture and value systems in which he or she lives and in relation to goals, expectations, standards and concerns. It is affected in complex ways by the person's physical health, psychological state, level of independence, social relationships and how the person relates to salient features of his or her environment.'*
>
> (World Health Organisation, 1998) [445] pg 1569

It seems likely that if malnutrition negatively impacts on HRQoL, the use of nutritional support may subsequently improve HRQoL [446]. The body of evidence to date is however limited.

There is only one published RCT to date studying the effect of nutritional support on HRQoL in GI surgical patients post-operatively. Beattie *et al* (2000)[447] conducted an RCT studying the effect of EN on nutritional status, morbidity and HRQoL in surgical patients, post-operatively. Patients were randomised to either a 1.5-kcal/ml oral supplements or standard management (nil by mouth). They concluded that the oral enteral supplements improved nutritional status, reduced complications and improved HRQoL (using the UK SF-36 questionnaire).

Similar improvements were reported in HRQoL in chronic illness [448] and in head and neck cancer surgical patients, who received nutritional support [449].

1.5.4 Summary of Section

This section has detailed the history behind the delivery of nutrition to surgical patients in particular. It discussed how the use of nutritional support seems to have tangible benefits on surrogate endpoints such as maintaining weight, muscle mass and function, improving oral nutritional intake, promoting immunological function and the inflammatory response. These effects also appear to manifest in improved wound healing, improved GIT function, improved immunological outcome and improved HRQoL. The next section will explore the clinical trials comparing different nutritional support modalities, paying particular attention to improvements in clinical outcome in surgical patients.

1.6 Nutritional Support and Clinical Outcome in Surgical Patients

1.6.0 Introduction

The previous section suggested that nutritional support alters physiological function. This has raised the expectations of clinicians working in the field of nutritional support to assume that nutritional support must therefore improve clinical outcome.

Twenty years ago, a review paper entitled 'What supports Nutritional Support' [450] concluded that the trials in nutritional support were not scientifically robust and adequately powered to produce a radical change in surgical clinical practice. Since this, subsequent trials, meta-analysis and systematic reviews of nutritional support (both EN and TPN) still remain inconclusive as to the optimal route of delivery of nutrition peri-operatively.

Some of the meta-analyses have combined trials of EN with other nutritional interventions such as oral diet and sip feeds [451, 452]. These reviews therefore have heterogeneous study populations, making the generalisability of the findings difficult. At the time of completion of this thesis there were no systematic reviews of peri-operative nutritional support in major upper gastrointestinal surgery in the Cochrane library.

1.6.1 Current Use of Nutritional Support in the United Kingdom

The use of nutritional support therefore remains a controversial post-operative, therapeutic intervention in surgical patients. Currently, its use remains *ad hoc* in many UK hospitals [59, 60]. Many patients remain 'nil by mouth' for the first week post-operatively. This may predispose patients to the effects of malnutrition and its subsequent patho-physiological consequences as discussed in section 1.3.

Parenteral nutrition (PN) is a frequently used option for providing patients with nutritional support post-operatively. However, its use tends to be delayed and initiated only after the development of major surgical complications.

The next section will provide a review of RCTs and meta-analyses of nutritional support. It will be presented as follows:

1. Pre-operative nutritional support versus post-operative nutritional support

2. Enteral nutrition (EN) versus Parenteral Nutrition (PN)

3. Pre-operative PN versus STD hospital management

4. Post-operative PN versus STD hospital management

5. Peri-operative PN versus EN

6. Post-operative EN versus STD hospital management (i.e. nil by mouth and IV fluids).

1.6.2 Literature Search Strategy

The following databases were searched: Medline 1966-2008; CINAHL 1982-2008; EMBASE 1980-2008; Cochrane Library. The medical subject headings (MeSH) nutrition, nutrients, diet, nutritional support, feeding, feed, parenteral and enteral was used.

The search was limited to RCTs, meta-analyses and systematic reviews. The titles and abstracts were scanned to remove irrelevant papers. The search was further limited to the MeSH headings operative, surgical, surgery, resection and the text words clinical outcomes, morbidity, complications, hospital stay.

In addition, key RCTs reference lists were hand searched to determine any titles that were relevant. This produced:

1. 13 RCTS for perioperative TPN versus standard management
2. 13 RCTs for Enteral Nutrition versus Total Parenteral Nutrition
3. 13 RCTs for Enteral Nutrition versus Standard management

The methodological quality criteria for reviewing the trials are presented in appendix I.II. In the following section, tables 1.6.1 to 1.6.4 include all RCTs conducted to date for the above classification. The RCTs are classified in the tables as follows:

* Poor quality trials. Inadequate power secondary to small sample size; failure to report stringent randomisation techniques i.e. reporting the methods of random sequence allocation and also methods of allocation concealment.

** High quality trial. Report allocation concealment and methods of determining random sequence were robust

*** Meta-analysis or systematic review of RCTs.

1.6.3 Pre-operative Nutritional Support versus Post-operative Nutritional Support

Studies have compared the use of pre-operative nutritional support versus post-operative nutritional support. It is important prior to appreciate that a patient prior to surgery is metabolically very different from an immediate post-operative patient. Pre-operative patients are typically metabolically stable, however, patients who are to undergo surgery for a malignancy are arguably not metabolically stable, as the effects of cancer cachexia may alter metabolism. In contrast, patients in the immediate post-operative phase are catabolic, losing cellular protein, gaining extracelluar fluid and have a decreased plasma protein concentration, all mediated by the acute phase response (sections 1.2.2.1 and 1.2.2.2).

1.6.4 Enteral Nutrition versus Parenteral Nutrition

To date, there appears to be no simple answer to the question of which is superior - parenteral or enteral nutrition. It is important to realise that there are fundamental differences between the two modalities.

The obvious difference being that EN uses the GIT, therefore, it is assumed to be more 'physiological' than PN. Normal feeding in humans is associated with periods of high nutrient intake followed by periods of no nutrient intake. This results in a fed/fast cycle. Thus, the continuous infusion of nutrients either EN or PN is not 'physiological'. Therefore, the rather simplistic view often perceived by many clinicians that enteral is a non-scientific or 'basic' modality for treatment is not so. A review of the studies of the comparing enteral and parenteral nutrition is outlined later in this section.

1.6.5 Peri-operative Parenteral Nutrition versus Standard Hospital care

Thirteen RCTs [278, 279, 354, 356, 453-461] and 2 meta-analysis [462, 463] have compared peri-operative PN (i.e. pre and post PN combined) versus STD hospital management. These are presented in table 1.6.1.

Seven studies [279, 354, 356, 456-459] concluded that patients who had peri-operative PN developed fewer post-operative complications than the control group; in three of these studies [354, 457, 458] the difference was statistically significant. Two studies demonstrated a reduction in mortality [459, 461] with pre-operative PN versus controls. The difficulty with critiquing these trials is the variation in the use and definition of STD management. This STD management could be *ad hoc* oral intake or enteral tube feeding. Thus, interpretation of these RCTs and meta-analysis must be with caution.

The Veterans Affair Administration [278] randomised peri-operative patients to either pre-operative PN for 7-15 days, which was continued for 3 days after surgery, or oral diet as tolerated. The oral intakes were not reported in either group. The results suggest no difference between the 2 groups in overall complication rates (22.5% vs. 24.6% NS) and mortality (13.5% and 10.5% N.S). However, more infectious complications occurred in the TPN group (14.1% vs.

6.4%; p<0.01). Several causes may have contributed to the increased infection rates; the central venous catheter used to deliver the TPN, bacterial translocation or excessive calorie and glucose load precipitating hyperglycaemia. All of which have been suggested to increase bacterial infections. None of these were reported in the study.

The authors performed a sub-group analysis. The results of which indicate that patients with severe malnutrition who received TPN (N=50) reported significantly fewer non-septic complications (5% vs. 43% p=0.03) and total complications (21% vs. 47% p<0.05) as compared to STD hospital care. This study suggests that patients with severe malnutrition benefit from peri-operative TPN (manifested by a reduction in surgical morbidity) when compared to well-nourished patients. No benefit was noted in patients with mild or moderate malnutrition.

Three meta-analyses have pooled the data from these trials. One meta-analysis [462] concluded that pre-operative TPN improved morbidity and reduced post-operative mortality as compared to patients receiving standard care (normal hospital diet as tolerated).

A more recent meta-analysis [463] of 27 RCTs of peri-operative TPN in adult GI surgical patients reiterated these findings. It was concluded that TPN did not alter hospital mortality rates peri-operatively. However, there was a non-significant reduction in post-operative total complications in the TPN group (Relative Risk 0.81 (95% CI 0.65-1.01). The most significant reduction in complications was in patients with severe malnutrition (relative risk 0.52 (95%CI=0.30-0.91)).

Another meta-analysis of 41 RCTs [464] in surgical patients in the peri-operative period concluded there is no benefit on post-operative mortality, clinical outcome or length of hospital stay in patients who receive TPN peri-operatively.

Details of the RCTs summarised above are listed in table 1.6.1.

Table 1.6.1 A review of the Randomised Controlled Trial Peri-Operative Parenteral Nutrition versus Standard Hospital Diet

Study	Methods	Participants	Interventions	Outcomes	Randomisation Methods
Bellantone *et al* 1988 [459]*	Prospective randomised trial	N=100 Various Gastrointestinal diseases requiring surgical procedure 37% of total patients were malnourished	2 groups TPN 30 non protein calories /Kg/day lipid 9kcals/kg/day for 7 days versus standard hospital diet	Septic Complications TPN 30% Control 35.3% (N.S) Mortality 2.5% vs. 3.9% No difference in the 2 groups in terms of mortality and complication rates.	Patients were not stratified for nutritional status No randomisation methods or allocation concealment reported
Bellantone *et al* 1988 [460]*	Prospective randomised trial	Gastrointestinal diseases requiring surgical procedure 100% of total patients were malnourished	2 Groups TPN 30 non protein calories /Kg/day lipid versus standard hospital diet	Septic complications TPN 14.8% vs. Control 7.8% (P<0.001) Mortality TPN 1.8% vs. control 2.2%	TPN group had more septic complications but a trend towards lower mortality. No randomisation methods or allocation concealment reported
Fan *et al* 1989 * [455]	Prospective randomised controlled trial	N=40 Oesophageal cancer Patients were matched for age sex and nutritional status, tumour staging or histology. 77% of patients were malnourished	2 groups Pre -op TPN >40 non protein calories/Kg/day for 7-10 days versus hospital diet	Complications TPN 85% vs. Control 75% (N.S) TPN group had a statistically significant improvement in weight gain but no differences in mortality	No randomisation methods or allocation concealment reported

Table 1.6.1 A review of the Randomised Controlled Trial Peri-Operative Parenteral Nutrition versus Standard Hospital Diet

Study	Methods	Participants	Interventions	Outcomes	Randomisation Methods
Heatley et al 1979 [354] *	Prospective randomised controlled trial Patients were randomised based on odds and even year of birth	N=74 2 groups Gastric and oesophageal cancer	Randomised pre-op to either oral diet n=36 or oral diet and TPN N=38. Study time was 7-10 days pre-operatively	Post-op complications: TPN group = 35.4% Control group= 83% Wound infection rates TPN group=7.7% and 30.5% in the study group (P<0.05) Mortality rate was the same in both groups Concluded that TPN was not of benefit to out way the complications of the catheter.	The authors concluded that 25/38 had to have TPN catheters changed during the study period due to catheter complications. Allocation Concealment not reported. Randomisation methods not robust.
Holter and Fischer 1977 *[356]	Prospective Randomised Trial. Randomisation methods used random number tables	N=56 randomised to receive either pre-op TPN or oral diet.	Patients were stratified for pre-operative nutritional status.	Post-op complications in malnourished patients reduced from 19.2 % to 13.3% (Not significant)	Study generally well designed but degree of type II error. Allocation Concealment not reported
Meguid *et al* 1988 [458] *	Prospective, randomised controlled trial	N= 160 100% malnourished. Patients with Gastrointestinal Cancers	Pre-operative TPN 35 Non Protein Calories/KG/day for 8 days versus standard hospital diet followed by post-op TPN in all patients	Post-op complication rate; TPN N =10/32 (31.3%) standard group 19/34 (56%) (p<0.03) Mortality TPN 3% vs. 0% in Control	Allocation Concealment not reported. Randomisation methods not robust.
Moghissi *et al* * 1977 [457]	Prospective randomised controlled trial	N=22 Patients with oesophageal cancer (100%	2 groups patients were given either TPN (40-50 Non Protein Calories/kg/day) or	All patients in the pre-operative TPN group were in +ve nitrogen balance and patients on IV fluids were in a -ve nitrogen balance.	Allocation Concealment not reported. Randomisation methods not robust.

Table 1.6.1 A review of the Randomised Controlled Trial Peri-Operative Parenteral Nutrition versus Sta

Study	Methods	Participants	Interventions	Outcomes
		malnourished)	standard management	Patients in the TPN had impro in wound healing but not signif TPN group 0% complications a control group had 80% complic rate (p<0.05)
Muller *et al* 1986 [461] *	Prospective randomised trial.	N=125 Gastro/oesophageal Cancer surgery	2 groups TPN (2400kcals) for 10 days or oral diet as tolerated Equal number of malnourished patients in each group	Post-op Complications; TPN= Control = 11% (p<0.05) Mortality rates= TPN =3% Con 11% (p<0.05)
Mullen *et al* 1981 [454] [456] *	Prospective randomised controlled trial	N=145 with GI malignancies	2 groups: TPN group for 10 days or standard hospital diet. Patients were matched for nutritional status.	TPN had a significant reductio complications and mortality wh compared to oral diet
Smith and Hartemink *et al* 1985 * [358]	Prospective randomised controlled trial	N=34. All malnourished using the PNI (Mullen et al, 1979)	2 groups TPN group 50-60 NPCs/KG/day for 6-14 days pre-op versus standard hospital diet pre-op	Major Complications rate; TPN Control Group= 35.3% (no sig) Mortality Rate TPN=5.9% and (no sig) TPN did have a improvement i nutritional status (p<0.05)

Table 1.6.1 A review of the Randomised Controlled Trial Peri-Operative Parenteral Nutrition versus Sta

Study	Methods	Participants	Interventions	Outcomes
Thompson *et al* 1981[453] *	Prospective randomised controlled trial	N=21 100% Malnourished Patients with GI cancer undergoing surgery	2 groups TPN 40-50 NPCs/KG/day for 8-15 days pre-op versus group with standard hospital diet	Complications rates, TPN 16.7 Control group 11.1% (N.S). No change in mortality (0% TP 0% Control)
Veterans Affair 1991 [278] *	Prospective randomly assigned to 2 groups Randomisation methods used computer generated random sequence.	N=395 100% malnourished Undergoing laparotomy or non-cardiac thoracotomy	2 groups TPN 7-10 days before surgery and 3 days after wards Control Group received Standard and IV fluids as needed. The control group could then start oral diet, TPN or TEN as required at 3 days post-op.	Post op Complications were si both groups. (TPN 25.5% vs. 2 The patients categorised as se malnourished had fewer non-infectious complications then c (5% vs. 43% p=0.03)
Von Meyenfeldt *et al*1992 [279] **	Prospective randomised trial	N=101 100% malnourished GI cancer surgical patients	2 groups; TPN 35-40 NPCs/KG/day for 10-23 days versus standard hospital diet and treatment	Complications rates; TPN 12% vs. Control 14 % (N. No change in mortality (4% vs. N.S)

Study	Methods	Participants	Interventions	Outcomes
Heyland [463] ***		Meta-analysis of 27 randomised controlled trials. N=2901 Adult GI surgical patients. No effect of TPN when compared to conventional interv rates.		
Klein [462] ***		Klein et al, 1997 pooled these results for a meta-analysis and found that the relati reduction in complications rates with pre-op TPN. (A reduction from 40%-30%). T and Enteral Nutrition (ASPEN) has recommended that the following patients may 1) Severely malnourished prior to surgery 2) Well nourished prior to surgery but undergo surgical treatment rendering them 14 days 3) Well nourished but due to the developments of complications will fail t 10-14 days. One flaw is they failed to define malnutrition and did not describe how nutritional s .		

* Poor quality trial design; i.e. small sample size, no robust outcome definitions or treatment allocation

** Clinical trials with adequate power and concealment allocation reported.

*** Meta-analyses

1.6.6 Post-operative Parenteral Nutrition versus Standard Hospital Management

Eight RCTs [355, 356, 465-470] and three meta-analysis [329, 471, 472] have compared the use of post-operative TPN with standard hospital management. The reviews are presented in table 1.6.2.

The largest two trials Sandstrom *et al* (1993)[469] (N=300) and Brennan *et al* (1994) [470] (N=114) reported a significant increase in major post-operative complication rates with the use of post-operative TPN. Three RCTs [355, 356] [466] however did report a reduction in total complications with post-operative TPN. Reference needs to be made to the high incidence of general complications in both groups, with 90% of the controls developing complications in the RCT by Collins *et al* (1978)[355].

A meta-analysis by Torosian (1999) [471] who combined data from previous RCTs reports that there was an increased complication rate of 10% in major GIT surgical patients who routinely received post-operative TPN. The conclusion was that TPN routinely in the immediate post-operative period is contraindicated. Table 1.6.2 presents details of the RCTs to date of post-operative parenteral nutrition versus standard management. There are general inconsistent conclusions from each of the RCTs, therefore, a consensus of whether post-operative parenteral nutrition is superior to standard management is not possible.

Table 1.6.2 A review of the Randomised Controlled Trial comparing Post-operative Parenteral Nu Management

Study	Methods	Participants	Interventions	Outcomes
Brennan *et al* 1994 [470] *	Prospective randomised controlled trial	N=117 100% pancreatic resection for cancer 100% malnourished	2 groups TPN 30-35 Non Protein Calories/kg/day for 12 days post-op versus standard group who received IV fluids until normal oral diet allowed	Total Complications TPN 45 % versus Control group 22.8% (p<0.002) Mortality increased 3-fold in patier receiving post-op TPN .
Collins *et al* 1978 [355] *	Prospective Randomised Controlled Trial	N=20 Major Surgical patients	2 groups TPN 37 Non Protein Calories/kg/day for 13 days post-op versus control group who received IV fluids	Total Complications 20 % TPN versus 90% Control group (p<0.01).
Holter and Fischer 1977 [356] *	Prospective Randomised Controlled Trial	N=30	2 groups TPN 30 Non Protein Calories/kg/day for 10 days post-op versus control group received IV fluids	Total Complications 13.3 % TPN group versus 19.2% Control group (N.S)
Jenson and Ginnerup 1982 [466] *	Prospective Randomised Controlled Trial	N=20	2 groups TPN for 6 days post-op versus control group who received IV fluids until oral diet	
Pershaw *et*	Prospective	N=47	2 groups	Total Complications

Table 1.6.2 A review of the Randomised Controlled Trial comparing Post-operative Parenteral N Management

Study	Methods	Participants	Interventions	Outcomes
al 1979 [465] *	Randomised Controlled Trial.	100% elective colonic resection.	TPN 40 Non Protein Calories/kg/day for 5 days post-op versus control group received IV fluids until oral diet	TPN 33.3 % versus Control group 17.4% (N.S).
Reilly *et al* 1990 [468] *	Prospective Randomised Controlled Trial	N=28	2 groups TPN 35 Non Protein Calories/kg/day for 7 days post-op versus control group received IV fluids until oral diet	Nothing recorded for Complication rates only surrogate endpoints
Sandstrom *et al* 1993 [469] *	Prospective randomised controlled trial	N=300. Emergency or elective major surgeries were eligible. Various types of surgery.	2 groups TPN 29 Non Protein Calories /kg/day for 9 days post-op (commenced day1 post op) versus control group who received IV fluids	Total Complications TPN 27.3 % versus control 16% ($p<0.05$)
Woolfson and Smith 1989 [467] *	Prospective double blind parallel study.	N=122 undergoing oesophago-gastrectomy or total cystectomy	2 groups TPN 35 Non Protein Calories/kg/day for more than 6 days post-op versus control group who received IV fluids.	Total Complications TPN 9.7 % versus Control group 6.7% (N.S)

Table 1.6.2 Characteristics of Meta-analyses comparing Post-operative Parenteral Nutrition and St (continued)

Torosian *et al* 1999 [471]	Torosian 1999 combined the data from 8 trials to reveal an increase in complications (10%) in p post-operative TPN in patients undergoing GI surgery. Therefore routine use of TPN post-opera
Campos and Meguid [329]	This was a meta-analysis of peri-operative nutritional support Date 1977-1991 N=22 prospective studies9/22 (40.9%) = pre-operative TPN vs. oral diet. 2/22 (9%) pre-operative TPN vs. EN 4/22 (18.1%) post-operative EN vs. oral 2/22 (9%) post-operative EN vs. oral 5/22 (22.7%) EN vs. TPN The authors assume that nutritional requirements are achieved in each group as this was not d
Detsky *et al* [472]	Detsky 1987 carried out a meta-analysis of trials of peri-operative nutritional support. They conc supplementation did reduce morbidity (reduced by 21%) and reduced post-operative mortality b however patients who received parenteral nutrition had increase complications when compared nutritional support (TPN increased by 7%).

* Poor quality trial design; i.e. small sample size, no robust outcome definitions or treatment allocation

** Clinical trials with adequate power and concealment allocation reported.

*** Meta-analyses

1.6.7 Peri-operative Enteral Nutrition versus Parenteral Nutrition

Over the last two decades, evidence has accumulated that EN may have advantages over PN. The advantages stem from the trophic effect of EN on the GIT. These have been discussed in section 1.5.1.5.

Recently published work by Kudsk (2002) [46] and Genton (2003) [47] have provided new insight into the protective mechanism of EN. The delivery of EN is thought to stimulate the production of neuropeptides produced by neurons located in the enteric nervous system. Neuropeptides are responsible for the initiating the cascade of cytokine and immunological response, in particular producing alterations in Gut Associated Lymphoid Tissue (GALT).

A study by Cunningham (1995) [473] reiterated this possible mechanism, demonstrating that lack of EN or the use of PN produced a reduction in cholecystokinin (CCK). CCK is a neuropeptide, which directly stimulates the enteric nervous system. Interestingly, when PN was supplemented with CCK prevention in changes in GALT occurred. Neuropeptides bind with immune cells located in the M-cells in the Peyers patches lining the distal small intestine, to heighten immune response. This has not been studied in humans as yet.

TPN also carries the risk of central venous catheter infection, alters liver function and has increased costs [40]. The recommendation for clinical practice should be to use EN (either oral or enteral tube feeding) in patients who require nutritional support, if the GIT tract is accessible and functioning. The problem with this statement centres on what constitutes and defines a functioning GIT tract. Many surgeons and clinicians consider that EN is not feasible, practical or safe in the early post-operative phase due to altered GIT motility and functioning. However, several cohort studies as presented in table 1.6.4 have demonstrated that EN is both practical and feasible in the early post-operative period. The next section will review the literature regarding the use of EN versus TPN post-operatively.

To date, thirteen RCTS have examined the clinical outcome of patients who were randomised to receive either EN or TPN post-operatively [52-58, 279, 359, 361, 381, 441, 474]. There are two meta-analyses [475, 476]. In seven RCTs, EN post-operatively delivered into the duodenum or jejunum was advantageous in improving clinical outcome when compared to PN post-operatively [52-57]. Length of hospital stay (LOHS) was reduced in the EN group as compared to the TPN group in two RCTs [58] [52]. Conversely, no difference in either clinical outcome or length of hospital was reported in three RCTs [279, 441, 474]. In another three studies, it was not possible to draw any conclusions as to the effect of EN on clinical outcome, as these studies reported nutritional outcomes only [359, 477, 478].

One of the limitations of many of the RCTs comparing EN and TPN is that the groups were not matched for isoenergetic and isonitrogenous feeding regimens post-operatively. A study [381] in patients (N=257) undergoing curative surgery for upper GI cancer compared early EN (24.4 kcals/kg/day) with PN (23kcals/kg/day). No differences were reported between the two groups in the overall study population. In a sub group analysis of the malnourished patients (N=91)(weight loss greater than 10%) there was a trend towards a lower complication rate in the EN group (37.1%) as compared to the PN group (52%) (P=0.023). There was also a significantly shorter length of hospital stay in the EN group versus the PN group (p=0.042). The authors commented that EN was four times less expensive than PN. This study suggested that malnourished cancer patients undergoing major upper GIT surgery had an improved clinical outcome with early EN as opposed to TPN post-operatively.

The findings of the study by Braga *et al* (2001) [381] were similar to a large study (N=307) of patients with 13-14% weight loss undergoing major GIT resection for cancer [52], EN or PN was commenced on day 1 post-operatively. Mean energy intakes were 26kcals/Kg actual body weight per day and 1.4g amino acid per kg/day for both the PN and EN groups. EN reduced post-operative complications as compared to PN (EN 34% versus PN 49% (p=0.005; risk differential 15%

p<=0.02). Length of hospital stay was also lower in the EN group, (13.4 days versus 15 days (p=0.009)). An important aspect of this study was that 8% of patients (N=14) did not tolerate EN post-operatively. All were subsequently commenced on TPN and analysed on an intention to treat basis.

The 2 meta-analyses, Moore *et al* (1992) [476] and Braunschweig (2001) [475] reported that EN improved clinical outcome when compared to PN. Moore *et al* (1992) [476] concluded that EN reduced septic complications when compared to PN (18% versus 35%; p=0.01), whilst Braunschweig (2001) [475] aggregated the results of 27 RCTs, to conclude there was a significantly lower risk of infections with EN than with PN (RR 0.64; CI 0.54-0.76). Interestingly, a third group receiving standard care had lower rates of infection than the TPN group.

A review paper by Bozzetti *et al* (2002) [479] concluded that post-operative EN is considered to be superior to PN, however the EN had to be adequate providing an adequate nitrogen supply (1.4g amino acids/kg/day).

Table 1.6.3 A review of the Randomised Controlled Trial comparing Post-operative Parenteral an

Study	Methods	Participants	Interventions	Outcomes
Aiko *et al* (2001) [58] *	Prospective randomised controlled trial	Japan. N=24 undergoing oesophagecto my	2 groups; ETF (N=13) commenced on the 1st post-op day vs. TPN (N=11). TPN and EN and TPN regimens were isocaloric and isonitrogenous	No differences in complications between tl groups LOHS ETF 34 days vs. T 40 days
Baigrie *et al* (1996) [53] *	Randomised prospective controlled trial.	Australia (1992-1994). N= 97. 100% oesophagecto my and gastrectomy.	2 groups. TPN N= 50 EN N=47. TPN via a central venous catheter commenced day 1 post-op EN via a jejunostomy (Witzel) commenced on day 3 post-op day using 5% dextrose. EN commenced day 4 at 100ml/hr.	Mortality rates TPN 12% versus TEN 8.5% Major Complications TPN 30% versus TEN 19% Minor complications TPN 22% versus EN 17% N.S.
Bower *et al* (1986) [54] *	Prospective Randomised Controlled Trial	N=20 100% GI or HPB surgery	2 groups EN N=10 NCJ and elemental feed commenced on Day 1 post-op for 7 days per day or TPN N=10 1000-3000kcals via a CVP for more than 7 day	ETF had better outcome TPN No statistical information paper Cost implications: patien charges for TPN group $2312.57, TEN group $849.40.

Table 1.6.3 A review of the Randomised Controlled Trial comparing Post-operative Parenteral and

Study	Methods	Participants	Interventions	Outcomes
Bozzetti *et al* (2001) [52, 381] **	Prospective Randomised Controlled Trial	N=307 100% malnourished	2 groups ETF N=159 versus TPN N=158	Post-operative complicat ETF =34% versus TPN 4 (p=0.005 CI 0.53-0.90) LOHS ETF 13.4 days vs. TPN 1 days (p=0.009)
Braga *et al* (2001) [55] [381] *		Italy N=257 Gastric N=121 Pancreas N=110 and N=26 Oesophagus.	2 groups EN (NCJ or NJT) N=126 versus TPN N=131 Both EN and TPN were isocaloric and isonitrogenous (25kcals/kg/day) and were continued unlit oral intake achieved 800 Kcals/day. ETF was commenced 6 hours post-op at 10ml/hr	Total complications ETF 35.7% versus TPN 40.4% (NS) No difference in LOHS, mortality, and infectious c non-infectious complicati TEN was four-fold less expensive than TPN ($25 $90.60/day)
Braga *et al* (2001)(b) [55] *	Prospective Randomised Controlled Trial	Italy N=166 (55.4% Gastric and 44.6% Pancreas 47% were malnourished.	3 groups EN (standard) N=55 IMN (IMPACT immunonutrition) N=55 TPN N=56	Overall infective complica rate was 38.4% ETF vs. IMN vs. 42.8% TPN LOHS= EN 16.1=/-5.9 vs 13.7 +/- 4.8 IMN vs. 17.5 6.1 TPN.
Heylen *et al* (1987) [478] *	Prospective Randomised Controlled Trial.	N=20 100% Total Gastrectomy.	2 groups EN N=10 versus TPN N=10. EN group had a NCJ. Elemental Feed (Vivonex) commenced 6 hours after surgery in EN. TPN group commenced 6 hours post-	No catheter complication either group. Anthropome measurements, lab and cellular immunity tests showed clinical benefit of Low cost and easy nursir

Table 1.6.3 A review of the Randomised Controlled Trial comparing Post-operative Parent

Study	Methods	Participants	Interventions	Outcomes
			op.	with EN
Lim *et al* (1981) [477] *	Prospective Randomised Controlled Trial	N= 24 100% oesophageal or gastric resection for cancer	2 Groups ENN= 12 TPN N=12 EN for 3 weeks via a gastrostomy and TPN for 3 weeks	TPN group had higher w gain. No significant difference between the 2 groups
Muggia-Sullam *et al* (1985) [359] *	Prospective Randomised Controlled Trial	USA N=15 100% Abdominal Resection	2 groups: ENN=7 via a NCJ (elemental nutrition) vs. TPN (N=8)	EN group had no complications with NCJ No outcome data compa the 2 groups
Okabayashi *et al* (2006) [56] **	Prospective Randomised Controlled Trial	Japan N=39 100% pancreatic resection for cancer	2 groups. All matched pre-operatively. TPN for 7 days N=23 EN(NCJ) day 1 post-op	Less pancreatic fistulas i group 6.3% versus 39.1 LOHS TPN 44.3+/-19 days vers EN 31.7+/-8.8 days (p=0.0011) No differences in other postoperative complicati
Pacelli *et al* (2001) [474] *	Multicentre Prospective Randomised Control Trial	N=241 100% elective gastric, colon and pancreatic	2 Groups EN group N=119, TPN group N=122. EN (NCJ) N=81 (68.1%) NJT N= 38 (31.9%)	Major Complications NS EN and TPN, (37.8% an 39.3%). No difference in

Study	Methods	Participants	Interventions	Outcomes
		resection for cancer.	and TPN via central venous catheter. Feed delivered over 8.7+/- 5.9 days.	postoperative mortality ra EN 5.9% and TPN 2.5%.
Reynolds *et al* (1997) [441] **	Prospective randomised Controlled Trial	UK N=67 100% Upper GI Resection for cancer Patients were matched for demographics	2 Groups EN N=33 NCJ TPN (peripheral catheter) N=34 Feed delivered for 7 days post-op EN Osmolite at 30 ml/hr increased to 100ml/hr TPN 1800 NPCs/day	No differences in outcom
Sand *et al* (1997)[57] **	Prospective Randomised Controlled Trial	N=29 100% UGI resection for Malignancy	2 groups ETF N=13 (NJT) TPN N=16 (central venous catheter).	Complications EN 38% versus 50% TPN (NS) No differences in LOHS.
Von Meyenfeldt (1992) [279] **	Prospective Randomised Controlled Trial	The Netherlands. N=200 100%- GI surgery for cancer	Groups 1) TPN N=51 10 days of pre-op and post op TPN; 2) EN N=50 pre-op either oral or NG; 3) Control group N=50 100% malnourished no nutrition pre/post op; 4) N=49 well nourished no pre/post- op nutrition	No differences in total complications between th groups

Study	Methods	Participants	Interventions	Outcomes
Excluded Studies	**The following trials are excluded if they were not a RCT, or the sample population wa major GI resection or were a meta-analysis**			
Adams *et al* [480]	A prospective randomised clinical trial in patients with multiple trauma of central total paren nutrition by jejunostomy N=23. Nutritional support began on the first post-operative day and significant differences were detected between the 2 groups in age, sex, injury severity; hou prescription and complications rates were all comparable. The authors suggested that ETF with multiple traumas.			
Braunschweig *et al* [475]	Meta-analysis of enteral compared with parenteral nutrition. Twenty-seven studies in 1828 showed a significantly lower relative risk of infection with tube feeding and standard care th is higher and risk of infection is higher with standard care than PN in malnourished populati			
Fletcher *et al* [481]	A prospective randomised controlled trial of enteral nutrition given via a NGT commenced a versus conventional management receiving IV fluids in patients undergoing major aortic gra between the groups in length of hospital stay and complications.			
Kudsk *et al* [482]	This study investigates the importance of nutrient administration after blunt and penetrating to either enteral or parenteral nutrition within 24 hours of injury. Both feeds were identical in carbohydrate. The enteral group had significantly fewer pneumonias (11.9%-31% p<0.02) intra-abdomina p<0.04) The benefit of enteral nutrition was more pronounced in the most severely ill patients.			
Moore *et al* [483]	This meta-analysis combined data from 8 prospective RCTs (N= 230) designed to compare TEN (N=112) in reducing septic complication in patients undergoing surgery or admitted wit via NCJ (N=81) NGT/NJT (N=37). All received an elemental type feed. All TPN was standa demonstrated that EN patients had fewer septic complications when compared to TPN (18			

* Poor quality trial design; i.e. small sample size, no robust outcome definitions or treatment allocation not defined.

** Clinical trials with adequate power and concealment allocation reported.

*** Meta-analyses

1.6.8 Early Enteral Nutrition versus Standard hospital management

So far, comparisons of TPN (pre-operatively and post-operatively) and STD management have suggested that TPN is not beneficial unless the patient is severely malnourished (Veterans Affair study (1991) [278]. Subsequently, the comparison of TPN versus EN indicates that EN is superior in terms of improving clinical outcome, reducing LOHS and reducing costs as compared to TPN.

Several meta-analysis have suggested that normal food intake or EN may be beneficial in reducing infective complications and LOHS in general patients [17] [415, 484-486]. However, the issue of the early introduction of oral food intake in patients with an upper GIT anastomosis is not straightforward, with minimal data available on the introduction of oral food intake in patients undergoing oesophagectomy, gastrectomy and pancreactectomy. One study, Lassen *et al* (2005) [487] page 346 concluded that:

> *" The paucity of evidence is reflected by the marked heterogeneity in practice across Surgical Units in Europe. Large groups of patients may be treated sub-optimally. Best perioperative care for these patients must be defined and documented. Especially, the role of early enteral/oral intake at will in upper GI surgery needs to be clarified by sufficiently powered trials."*

This review advocates the use of oral food at will, however certainly for many patients this may not be the preferred method. For patients the anorexia and lack of confidence with regards to eating certainly in the first few days post-operatively, is not a viable option. In these patients, the use of feeding jejunostomy, for immediate EEN may be the option in clinical practice. Studies have reported that immediate postoperative EN is safe, well tolerated and has advantages over traditional management with IV fluids or PN [13, 17, 57, 58, 488, 489]. However, doubt remains as to its efficacy and effectiveness in clinical practice.

A study has shown that jejunal EN increased GIT side effects, major complications and was associated with occasional fatal complications [66]. Conversely, a study illustrated that EN was not associated with any increased risk of aspiration pneumonia, abdominal distension, increased nausea or vomiting [490]. The section will discuss the feeding jejunostomy and review the cohort studies which have examined its use.

1.6.8.1 Feeding Jejunostomy

There are several methods of delivering EN post-operatively. Jejunostomy is a surgical procedure by which a tube is situated in the lumen of the proximal jejunum, primarily to administer nutrition, fluid and medication [491] reducing the need for central venous access for administration of nutrition and drugs.

The first jejunostomy for delivering nutrition was described by Busch in 1858 [492]. Several other surgeons in the late 1800s' [493-495] performed jejunostomies in patients with pyloric obstruction. One author [494] described,

> *"A mid-line was made and the jejunum brought into the wound. The jejunum was sewn to the wound with a double row of silk sutures. The patients received enemas of beef-tea and egg digested with Bengers's liquor pancreaticus every 4 hours, on day 2 the patients had injected digested beef tea and cream injected into the jejunostomy"*
>
> Surmay (1878*) page 325*

The patient subsequently died 36 hours later. A few years later in 1892, Maydl [496] performed a roux-en-Y jejunostomy; this allowed a feeding tube to be inserted for the delivery of nutrition.

The most commonly described technique was the Witzel jejunostomy. This was actually first described by Eiselberg in 1895 [497] but as it was a modification of the Witzel gastrostomy [498], it was continued to be called the Witzel Jejunostomy.

In 1973, Delany *et al* [73] inserted the first needle catheter jejunostomy (NCJ). They described the delivery of feeding and fluids via a NCJ in 42 patients undergoing UGI surgery).

Since this paper, many cohort and feasibility studies have reviewed jejunostomy feeding. Many reporting serious and occasionally life threatening complications [18, 63-65, 67, 70-72, 74, 75, 499-502]. A summary of these studies is presented in table 1.6.7.

A retrospective review by Adams (1986) [75] of jejunostomy feeding compared three types of feeding jejunostomy. The total number of major complications was high; ranging from 33% to 66.6%. The mortality rate attributed to all type of jejunostomy was 10%. The conclusion from this paper was that feeding jejunostomy is not indicated for patients post-operatively. However, comment must be made as to the exceptionally high complications and mortality overall, in this paper.

The complications seen with jejunostomy can be classified into mechanical, infectious, gastrointestinal, or metabolic.

1. Mechanical Complications such as tube dislocation, occlusion or migration

2. Surgical Complications such as cutaneous or intrabdominal abscesses, enterocutaneous fistulas, pneumatosis, small bowel obstruction, and intestinal ischaemia.

3. Infectious complications can occur such as aspiration pneumonia or contamination of the enteral feed.

4. Gastrointestinal intolerance to jejunal feeding is reported to be between 2.3% and 6.8% and include abdominal distension, colic, constipation, nausea, and vomiting.

5. Metabolic complications include hyperglycemia, hypokalaemia, water and electrolyte imbalance, hypophosphataemia, and hypomagnesaemia.

The largest prospective study over nine years was reported by Braga *et al* (2002) [66]. They studied a series of 650 patients undergoing GIT surgery. All patients had either a Needle Catheter Jejunostomy (NCJ) (61.8%) or Naso-Jejunal feeding Tube (NJT) (38.2%). Severe jejunostomy related complications were noted in 1.7% of patients. Enteral nutrition related mortality was 0.1%. One patient who had a NJT died of aspiration/ respiratory failure, directly attributed to the enteral feed. Refractory intolerance of the enteral feed was reported in 48% of patients. The authors recommended the intolerance could be minimized with the slow increase in feed rate in the first post-operative week and close monitoring. They concluded that EEN is safe and well tolerated and was not detrimental to anastomotic healing. The authors suggested that any intolerance of EN is an early predictor of impeding post-operative complications.

Another prospective cohort study [65] of 84 patients post major upper GIT surgery, commenced feed at 30ml/hr with a slow increase of feed rate to a maximum of 90ml/hr. No major complications were reported with 20% of patients having minor symptoms such as distension, nausea or vomiting.

Biffi *et al* (200) [64] studied 80 UGI cancer surgical patients who all received EN commenced at 15 mls/hour. The authors concluded that 1.25% of patients had minor complications such as nausea and distension that resolved after transient reduction in feed rate. No major complications were reported. Sarr (1999) [69] reviewed 500 patients who all received NCJ. Major complications associated with the NCJ were 0.6%. Minor complications (nausea, vomiting and distension) were reported in 15% of patients. Positive reports of NCJ were also reported in a multi centred pilot study of 56 patients [68] .

A study from the USA [503] had a 9% complication rate with the jejunostomy tube. This study did however use a Foley catheter as the tube of choice. A recent study from Ireland [70] prospectively studied 205 patients post oesophagectomy. They concluded that early EN via a NCJ was tolerated in 92% of patients. Patients were fed on average for 15 days with 26% requiring long term nutritional support i.e. for longer than 20 days. Serious complications were reported in 1.4%

of patients all requiring re-laparotomy. There was one death directly attributed to jejunostomy feeding.

Table 1.6.4 below provides an overview of the studies of jejunostomy tube feeding. The percentages of major complications associated with the jejunostomy are presented, in addition to the fatal complications. Several of the studies used a Foley catheter for the jejunostomy tube. The percentages of major complications range from 0% to 40%. Mortality associated with the jejunostomy tube ranges from 0% to 10%.

Table 1.6.4 Review of Studies of Jejunostomy Tube Related Complications

Author	N	Major Complication Jej%	Minor Complications jejunostomy (%)	Mortality associated with jejunostomy (%)	Type of Jejunostomy
Delaney *et al* (1977) [73]	42	Not reported	Not reported	Not reported	NCJ
Smith *et al* (1985)[358]	50	20/50	Not reported	1/50	NCJ
Adams *et al* (1986) [75]	73	40	10	10	Stamm(46)Maydl(9)Witzel (17)
Smith-Choban (1986) [500]	143	10/143	55	5/143	Foley catheter
Brandmair and Lehr (1988) [504]	40	-	45	Not reported	Not reported
Gernt and Orringer (1994) [505]	523	2.1	2.1	Not reported	Witzel style jejunostomy
Wakefield *et al* (995) [72]	58	0	2	0	NCJ-Fresenius freka
Myers *et al* (1995) [499]	2072	1.5	0.74	0.15	Not reported
Mercer and Mungara (1996)[488]	32	30	Not reported	Not reported	Foley catheter
Eddy *et al* (1996) [63]	122	9.8	9.8	0	NCJ
Sonawane (1997) [71]	96	8.3	7.2	3.2	NS
Velez *et al* (1997) [68]	56	0	19.5	0	NCJ
Heslin *et al* (1997) [503]	160	4	9	0.5	Foley
Yagi (1999) [506]	78	0	3.8	0	Witzel type (silicon catheter)
Senkal *et al* (1999) [507]	154	Not reported	18.2	Not reported	NCJ
Sarr 1999 [69]	500	0.6	15	0	NCJ
Biffi *et al* (2000) [64]	80	0	1.25	0	NCJ
Braga *et al* (2002) [66]	650	1.7		0.1	NCJ
Han-Geurts *et al* (2004) [67]	1,166	1.1	1	0.4	NCJ
Chin *et al* (2004) [65]	84	12.9	20	0	NCJ
Sica *et al* (2005) [74]	262	1.5	0.1	0	NCJ
Ryan *et al* (2006) [70]	205	1.4		0.5	NCJ

A study of 1,166 patients undergoing upper GI surgery had an overall post-operative complication rate of 36%. The complication rate attributed to the jejunostomy was 1.1% of patients. Mortality attributed to the jejunostomy was 0.4%. All these patients required re-laparotomy for intra-peritoneal leak [67].

Many of the studies above have made reference to the timings and increment of enteral feedings post-operatively. This was reiterated in a study by Holmes *et al* (1999) [508]. The authors suggested that the development of major jejunostomy related complications could be related to the feeding protocol used to initiate the feed. The authors concluded that too 'aggressive' feeding lead to GIT complications in particular 'distension necrosis'. This is a potentially fatal condition requiring urgent re-laparotomy. Aggressive feeding was defined as achieving nutritional 'goals' within 24-36 hours post-operatively. Other factors include osmolarity of the enteral feed, bacteria contamination and bacteria overgrowth of the small intestine secondary to H2 antagonists. A systematic review by Melis *et al* (2006) [644] details these as possibly aetiological factors.

The studies that have reported major and often fatal complications with needle catheter jejunostomy are summarised in table 1.6.5.

Table 1.6.5 Summary of Studies reporting fatal complications with jejunostomy feeding

Author	Complications	N with fatal complications	Comments
Gaddy *et al* (1986) [509]	Small bowel ischaemia	5	All had NCJ. and distension
Brenner and Schellhammer (1987) [510]	Small bowel necrosis	1	N=25 all post cystectomy
Rai *et al* (1996) [511]	Small bowel necrosis	2	N=2 jejunostomy used not specified
Lawlor *et al* (1998) [512]	Small bowel necrosis	3	N=3 NCJ
Scaife *et al* (1999) [513]	Small bowel necrosis	4	N=4 NCJ
Jorba *et al* (2000) [514]	Small bowel necrosis	5	N=5 NCJ
Zern (1985) [515]	Pneumatosis Intestinalis	3	N=2 Foley catheter
Schloerb *et al* (2004) [516]	Small bowel necrosis	5	N=15 all had water post-operatively
Smith *et al* (1985)[500]	Small bowel necrosis	5	N=144 Foley catheter

A study by Zapas *et al* (1996) [517] carried out a risk/benefit analysis comparing complication rates and avoidance of TPN, they concluded that the risk/benefit ratio was low and NCJ enteral nutrition was not to be recommended.

1.6.8.2 Nasojejunal (NJT) versus Needle Catheter Jejunostomy (NCJ) Nutrition

There is limited literature on the use of NJT vs. NCJ in clinical practice. One cohort review [66] of jejunal feeding showed that the NJT group (N=61%) had a higher rate of displacement and clogging than the jejunostomy catheter N=38.% (p=0.0005 and p=0.0007 respectively).

The main concern with the use of NJTs centres on patient compliance. It is reported that at least 50% of nasally passed tubes are voluntary or accidentally removed by the patients within a week of placement [61]. Patients also report that they found nasoenteral tubes to be more inconvenient and more uncomfortable than percutaneous tubes. This was despite the percutaneous tubes staying *in situ* for a longer period of time [62].

In patients undergoing pancreatic resection, a study [518] determined whether patients had reduced length of hospital stay who received double lumen gastrojejunostomy (GJT) tubes as compared to nasoenteral tubes. Insertion of a GJT was associated with a shorter length of hospital stay, reduced gastroparesis and was determined to be more cost effective.

1.6.8.3 Review of Randomised Controlled Trials of Early Enteral Nutrition versus Standard Post-Operative Management

The above section presented a review of the cohort studies of the feasibility of feeding jejunostomy. It is still not apparent whether the introduction of EEN within 24 hours of leaving the operating theatre improves clinical outcome and leads to a subsequent reduction in LOHS. The next section will examine the published RCTs to date.

Thirteen RCTs [12-16, 357, 358, 361, 483, 503, 518-521] have been published comparing EN versus STD post-operative management (nil by mouth) on the development of complications, clinical outcome and LOHS in patients undergoing major GI resectional surgery.

Four RCTs concluded that EN was beneficial in improving clinical outcome as compared to STD management [12-16]. Patients who received EN had a shorter LOHS of 3.5-5 days [12, 15, 16, 483, 518]. However, other RCTs [13, 14, 357, 358, 360, 416, 503, 519, 521] have refuted this. These studies have reported no reduction in LOHS with the use of early EN post-operatively.

Beier-Holgerson *et al* (1996) [12] (N=60) compared the use of EEN delivered via a NJT with Placebo (water). The author aimed to match the volumes delivered per day in each group. The study included all patients undergoing resection for GI disease. The studies conclude that the EEN group had a 3.5 days reduction in LOHS, and a lower mortality rate than the placebo group.

With regards to the development of complications, they demonstrated that EEN group had fewer total complications and a significantly lower incidence of postoperative infectious complications (7%) compared with the control group (47%) ($P<0.0009$) [12]. This is a high complication rate in the placebo group.

The choice of STD group intervention is a concern in some RCTs. The STD treatment used in the study by Beier-Holgerson *et al* (1996) was 900 mls of hypotonic fluids infused into the small intestines on the day of surgery. This may have led to influx of systemic fluid back into the intestines, subsequently

increasing pressure on the anastomosis, which may have had a contributory factor to the high incidence of complications in the STD group.

Heslin *et al* (1997) [503] conducted an RCT which examined the effect of EN on morbidity, mortality and LOHS in UGI cancer patients when given early postoperatively. After curative resection patients were randomised to receive either EN (n=97) or STD management, nil by mouth and intravenous fluids (n=98). There was a 5-6% preoperative weight loss in the sample suggesting some degree of malnutrition; serum albumin levels were within the normal range. No significant differences were reported in the two groups in relation to the incidence of major or minor complications, mortality rates or LOHS. Overall complication rate was 25% in both groups and overall mortality was 2.7%.

There were several confounding factors in this RCT. The patients randomised to EN group received approximately 30% of the planned EN goal in the first week. Post *hoc* analysis revealed that the EN group had more patients allocated who underwent surgical procedures with increased intra-operative duration time as compared to the standard group. Likewise, there were more patients who received neo-adjuvant chemotherapy allocated to the EN group. Thus the groups could be deemed non-equivalent for comparison. In summary, the results of this RCT need to be interpreted with caution, as the higher risk patients were allocated to the EN group.

The RCT by Watters *et al* 1997 [14] (N=40), also concluded that EEN was not superior to STD hospital management post-operatively. The results indicated that vital capacity, (which reflects respiratory muscle strength) was significantly lower in the EN group when compared to the unfed group postoperatively. The impairment was attributed to the high incidence of abdominal distension (62%) experienced in the EN group. This could have been related to the 'aggressive' feeding regimen of 2500 mls/day enteral feed to be delivered by day 2 post-operatively. It may be that the abdominal distension affected diaphragm function.

Lewis *et al* (2001) (2001) [17] performed a meta-analysis and systematic review of 13 RCTs comparing any type of enteral feeding with nil by mouth management after elective gastro-intestinal surgery. The majority of the RCTs had

heterogeneous samples or small size. The authors questioned the methodological quality of many of the studies included. The meta-analysis all included a range of routes of delivery of enteral nutritional support. In six studies, patients in the intervention group were fed directly into the small bowel, in five studies they were fed orally. The authors concluded that EN reduced LOHS by 1 day, compared to standard management. Early feeding reduced the risk of any type of infection. Risk reductions were also seen in anastomotic dehiscence, wound infection, pneumonia, intra-abdominal abscess, and mortality, but these failed to reach significance. The risk of vomiting was higher in the EEN group.

The following tables discuss the RCTs comparing postoperative early enteral nutrition versus standard hospital management (i.e. nil by mouth) in patients undergoing major gastrointestinal resection. Meta-analyses and RCTs of other groups of surgery are presented in the excluded trials section that follows.

Table 1.6.6 A review of the Randomised Controlled Trial comparing Postoperative Enteral N Management (i.e. nil by mouth)

Study	Methods	Participants	Interventions	Outcomes
Beier-Holgerson *et al* (1996) [12] **	Randomised double blind prospective trial. Informed written consent was obtained.	Denmark N=60. 15% patients malnourished Placebo Group=30. Gastrointestinal diseases for bowel resection with an anastomosis, an enterostomy, a gastric or oesophageal resection were included. Patients were stratified for pre-operative nutritional status.	All patients have a NJT *(Flocare)*. EN (N=30) received *nutridrink* (Nutricia Clinical Care, Netherlands) 600mls day of operation. Nutrition group= 30 NJT placed in 2nd-3rd jejunum. 900 Kcals and 30g protein; day 1 post-operative=1000kcals and 50g protein; day 2 post-operative 1400kcals and 80g protein and day 3 1800kcals and 100 grams protein; Control Placebo 600mls (water) increasing volume to 1000mls/day.	Major Complications EN 26% versus Placebo 63% (p=0.0089) Infectious complications EN 6.6% versus Placebo 46.6% (p=0.0009) LOHS EN 8 days versus Placebo 1 days (p=0.08) Mortality Rates EN 6.6 % versus Placebo group 13.3% Economic: EN 43.270 DKK versus Placebo group 58.385 DKK
Carr *et al* (1996) [13] *	Randomised Controlled Trial	UK N=30 100% Elective GI Resections	2 Groups EN: (n= 14) via a double lumen Medicina NJT commenced 2-3 hours post-op Control group: IV fluids (N= 14) until introduction of normal food.	No difference in LOHS (9.8 days vs. 9.3 days); EN group appears to have maintained Nitrogen balance in first wee post-op. Intestinal permeabil reduced in the EN group (p<0.005). EN had less naus vomiting and distension than the IVI group (NS).

Table 1.6.6 A review of the Randomised Controlled Trial comparing Postoperative Enteral Nutrition vers

Study	Methods	Participants	Interventions	Outcomes
Heslin *et al* (1997) [503] **	Randomised Controlled Trial	USA N=195 100% Major UGI surgery with curative intent. Oesophageal (N= 23), gastric (N=75), pancreatic (N= 86) or bile duct (N=11) cancer.	2 Groups EN group N= 97 Control group N= 98. EN commenced 24 hours post-op via NCJ, aiming towards 25 kcal/ kg per day, continued until oral intake resumed. Control patients had intravenous crystalloid solutions until commenced oral intake.	No differences in complicati rates or mortality. No difference on LOHS. Weight loss was the same ir groups, 5% EN and 6% Control.
Hoover *et al* (1980) [357] *	Prospective Randomised Controlled Trial	USA. 100% Oesophagectomy, gastroduodenal, biliary or pancreatic resections N=49	2 groups ETF (N= 27) NCJ with elemental feed (Vivonex) commenced day 0 Feed rate commenced at 50ml/hr increasing to 125ml/hr for a minimum of 10 days Control (N=22) IV fluids until oral diet commenced.	No differences in complicati Improved nitrogen balance i the ETF group. No weight loss ETF group compared to mean 4kg weig loss in Control group.
Mack *et al*	A prospective	USA N=59	2 groups	LOHS EN=11.5 +/- 2.9 days

Table 1.6.6 A review of the Randomised Controlled Trial comparing Postoperative Enteral Nut

Study	Methods	Participants	Interventions	Outcomes
(2004) [518] **	Randomised Controlled Trial	100% peri-ampullary tumours for PPPD 19 patients palliative at surgery	EN group N=20 double lumen NJT Control group N= 16 nil by mouth until oral diet	and control = 15.8 +/- 7.8 da p=0.01) Hospital charges were $82,151+/-56,632 in control and $52,589+/- $15,964 in t EN (p=0.036) Incidence of weight loss wa similar in each group. Delayed gastric emptying in control group =25%
Moore and Jones (1986) [483] *	Prospective Randomised Controlled Trial.	USA. N=75 GI surgical Procedure Study duration was 2 years. N=75 consecutive admissions. 12 were excluded from analysis (6 re-operations, 4 deaths, and 2 transfers to another hospital).	EN (N= 32) NCJ received elemental diet 18 hours after surgery and aiming for 3000 Kcals/day by day3. Control group (N=31) IVI fluids for 5 days and then TPN if no oral diet at that time.	Major complications in 15/3 (48%) of controls developed post-op complications. 14/31 (44%) had major complications. Septic morbi was greater in the control gr (29%) p<0.025. LOHS was shorter in the EN (25.3+/-6.1 days) Control gr (28.6 +/-6.1 days). Hospital costs were higher in the con group $609,000 (mean $19,636+/-3,396) compared $505,000 (mean $16,280+/- $2,146). Concluded that NCJ is safe, simple and feasible.
Page *et al* (2002) *	Prospective Randomised	UK N= 40 transthoracic	2 groups EN group N=20 either NJT	No difference in morbidity, mortality or any parameters

Table 1.6.6 A review of the Randomised Controlled Trial comparing Postoperative Enteral Nutrition v

Study	Methods	Participants	Interventions	Outcomes
[521]	Controlled Trial.	oesophagectomy for cancer Groups matched pre-operatively	(double lumen) or NCJ versus Control group N=20 EN feed started day 1 post-op at 25 ml/hr and increased every 4 hours until target volume was reached (35ml/kg body weight/day). Control group received IV fluids.	between the groups.
Sagar *et al* (1979)[15] *	Randomised Controlled Trial	UK N=30. 100% GIT Resection	2 Groups EN N=15 elemental diet via a double lumen into the stomach. Control group N=15 Iv fluids and after 2 days oral fluids and 'light' diet on day 6.	LOHS EN 14 days versus Control 1 days. Total complications EN 3 % versus 5% (NS). EN patients maintained their weight compared to controls (1.85kg) EN had improved nitrogen balance compared to control
Schroeder *et al* (1981) [16] *	Randomised Controlled Trial N=32	New Zealand 100% Small or large bowel resection	2 groups EN N =16 NJT feed given for 56 hours post-op Control group N=16 IV fluids until oral diet	LOHS:EN 10 days versus Control group 15 days (NS) Complications: 4 % versus 7 (NS).Higher wound healing rates in EN (NS)
Smith *et al* (1985) [358] *	Prospective Randomised Controlled Trial.	100% elective GIT resection for malignancy or bypass	2 groups EN N= 25 NCJ started 3 days post-op until oral intake adequate	No differences between the groups in total complications Failure due to catheter complications = 5/25 (20%)

Table 1.6.6 A review of the Randomised Controlled Trial comparing Postoperative Enteral Nutrition versu

Study	Methods	Participants	Interventions	Outcomes
		N=50 Duration =30 months	Control Group N=25 IV fluids until adequate oral intake.	Failure due to intolerance = 6/25 (24%) 14/25 successful feeding. 9/ failed enteral feed due to tub failure or intolerance. No recommendation for EN
Swails *et al* (1995) [522] *	Prospective Randomised Controlled Trial	N=25	EN=13 started immediately after surgery and control group routine care and advancement to oral diet	No major complications associated with the feeding catheter. A trend towards ETF having shorted LOHS N.S)
Watters *et al* [14] *	Prospective Randomised Controlled Trial	N=47 UGI Randomised patients N=31. N=16 not randomised as palliative at surgery. Groups matched at baseline	2 Groups EN =13 NCJ 2 patients excluded in the EN group because of major complications. vs. Control=15 nil by mouth until oral diet commenced	EN group had decreases in vital capacity and FEV1 thar control patients. EN not beneficial.
Yeung *et al* 1979)[361] *	Randomised Controlled Trial	N=40 100% GIT surgery	2 Groups EN N=20 elemental diet via NCJ versus control group N=20 intravenous fluids and nil by mouth	No change in groups for LOI or complications rates

Table 1.6.6 A review of the Randomised Controlled Trial comparing Postoperative Enteral Nutrition versu

Study	The studies below were excluded from the main table for the randomised controlled trials as th meta-analyses or non upper gastrointestinal surgery.
Beattie [447]	Randomised controlled trial evaluating the use of enteral nutritional supplements in postoperat patients. N=101 (52 treatment group, 49 control group) admitted for elective gastrointestinal or group were provided with oral dietary supplements, 1.5 kcal/ ml and 0.06 g/ml protein and were Control patients lost more weight. Anthropometry and QOL were similarly significantly different Incidence of complications differed between the groups, 13 controls, 6 in treatment group. Mor the control patients. Concluded that postoperative nutritional supplementation improved nutritional status, QOL and
Biffi *et al* [64]	N=80 oncological GI surgical patients. Age 18-75. Jejunostomy tube inserted as *per* Delaney [scheduled surgical procedure. Nutrition was commenced at 15 ml/hr and increase over 5 days nutritional support for 14 days. This paper demonstrated a 1.25 % early complication rate this was related to intolerance of the reducing the feed rate temporarily. No late complications were demonstrated (12month fu) however no mention if the tube was in receiving nutritional support.
Braga *et al* [66]	Prospective study of 650 patients treated with EEN via a NCJ or NJT after major intestinal surg Jejunal feeding was started within 12 hours of surgery and increased by 20ml/hr daily until nutr 61.8% of patients had a NCJ (Witzel technique) and 38.2% had NJT. One patient aspirated with an NJT and subsequently died of respiratory failure. GI adverse effects occurred in 30% of patients. Emphasised the importance of keeping feed ra slowly. 4.6% of patients needed to switch to TPN. Low serum albumin correlated with refractory intole intolerance in 48% of patients represented a early symptoms of intra-abdominal complications. Concluded that EEN was safe and well tolerated and did not show any deleterious effect on an
Bufo *et al* [414]	Non-randomised uncontrolled trial of 38 patients undergoing colorectal surgery. Supports the concept of early post-operative nutritional support. Speculation that early enteral reduces hospital costs. Details discussion of post-operative ileus and GI motility post colorecta

Table 1.6.6 A Review of the Trials comparing Postoperative Enteral Nutrition versus Standard Hos

Cerra *et al* [523]	Excluded as uses head injuries, long bone fractures N=9. Patients were classed as moderatel The study focused on small intestinal feeding in the presence of ileus and moderately high lev Poor study with small sample size. the paper does not give clear insight into objectives and ou
Chin *et al* [65]	York (UK). A prospective cohort study of 84 patients undergoing oesophagectomy, gastrectom for cancer. All patients had a NCJ by one of 2 dedicated surgeons as per technique by Sarr (1 needle catheter jejunostomy). The study was over 3 years. Feed was commenced within 24 h increasing to requirements by day 3, a rate of 60-90mls/hour. No patients had NCJ leakage th procedure related mortality. Complications (14%) related to feeding were managed by reducing feed rates. 98% of patients started nutritional support on day1 post-op. Feed rate commenced at 30ml/hr. 68% (N=57) achieved nutritional requirements in 3 days post-op. No major complications or deaths were reported in the study. Minor feeding related complications such as distension, nausea etc were 20%. Conclusions are that NCJ is safe despite being an invasive procedure when practised in exper
DeGottardi *et al* [524]	N=100 had NCJ for post-operative enteral nutrition. 26 developed catheter related complicatio due to feed leakage. No patients died as a result. N=18 developed nutritional related complications which resolved due to reducing the feed rate Concluded jejunostomy is safe and that complications can be reduced by meticulous insertion can reduce feed related complications.
Eddy *et al* (1996) [63]	N=122. Retrospective review of trauma patients. Complication rate of 14% (8% serious). Weal patients are prone to higher rate of complications associated with jejunostomy secondary to er the stoma site secondary to oedema due to acute post-injury response leading to leakage at th
Farreras *et al* 2005 [525]	Barcelona, Spain.N=66 A prospective randomised double blind clinical trial. One group receive (*Impact*). Control group received standard enteral nutrition (*Isosource)*. Concluded that immun surgical wound healing for patients undergoing gastrectomy and reduces general morbidity an infections.
Frankel and Horowitz (1989) [416]	N=50 randomised into two groups to assess the importance of the role of Moss Nasojejunal tu Treatment group had oesophago-gastric decompression and immediate post op enteral feedin treatment group, none in control. No difference in length of hospital stay or use of post op anal discharge complications in either group.

Table 1.6.6 A Review of the Trials comparing Postoperative Enteral Nutrition versus Standard

Lewis *et al* (2001) [17] ***	A meta-analysis and systematic review of RCTs comparing any type of enteral feeding with nil elective gastro-intestinal surgery. Heterogeneous RCTs and most very small and of doubtful m studies, patients in the intervention group were fed directly into the small bowel, in five studies reduced by 1 day in the EEN group. Early feeding reduced the risk of any type of infection. Risk reductions were also seen in anast infection, pneumonia, intra-abdominal abscess, and mortality, but these failed to reach significa higher in the EEN group.
Lobo *et al* 2006 [526]	Randomised double blind RCT. N=120 Patients undergoing major resection for cancers of the stomach. Two groups. One group had NCJ and enteral nutrition versus NCJ and immunonutriti days. Feeding commence 4 hours post-operatively at 25 ml/hour on day 0, 50ml/hour on day 1 groups. Analysed 108 patients (54 in each group). No difference in feed delivery in either group. Median LOHS was 14.5 days (12-23) in group A Infective complications were similar in both groups (44%). Jejunostomy related complications were 50% in either group. Authors concluded no benefit wit
Mercer *et al* (1996) [488]	N=32 undergoing palliative or curative surgery for oesophago-gastric carcinomas. Prospective the early post-operative period. All patients had a Foley catheter type tube. There were no post of jejunal feeding was 24 days. A cost of enteral nutrition was $188.71 per patient. Gastrointestinal complications occurred in 7 patients. Metabolic complications occurred in 3 pa Concluded that ETF is effective and safe and cheap. Excluded as not RCT
Ryan *et al* (1981) [18]	N=14 colorectal patients. RCTS 2 groups one enteral nutrition group and one control group rec complication in the nutrition group versus 43% in the control group.
Sarr *et al* (1999) [69]	A study of 500 consecutive cases in one hospital centre over a 10 year period. Insertion of NC (0.006%) major complications in patients requiring surgical treatment. Minor complications were shown in 15% of patients such as intolerance (diarrhoea and distens allow safer, cheaper and equally effective delivery of nutrition, compared to TPN after major ab
Senkal *et al* (2004) [527]	Prospective open clinical trial N=20 over 8 months. Cancer patients undergoing major elective 3 hours after surgery at 20-30 ml/hr via a NCJ (not mentioned which one). Total Kcals for 3 days = 500 Kcals/ day. On day 3 patients were additionally given (Reconvan F 250kcal/500mls, glutamine, and nucleotides. Concluded that the 'new ' feed as metabolically sa

	is well tolerated in surgical patients and provides a novel way to deliver conditional essential nu
Singh *et al* (1998) [360]	A 1-year prospective study to investigate the feasibility and efficacy of immediate postoperative intestinal perforation and peritonitis. Treatment group N=21 (Witzel jejunostomy) received ente operatively. By day 3 they were receiving at least 2 litres of full strength feed for 24 hours/d. The two groups were comparable except for higher sepsis score in treatment group. Treatmen balance by day 3, the control group remained in negative nitrogen b balance throughout. Diarrh was easily resolved. Mortality rates were similar. Control group 22 septic complications compa Concluded that immediate post op feeding is feasible.
Smedley [528]	N=179 were randomised to receive one of four groups: 1) no oral nutritional supplements 2) Pre-operative oral nutritional supplements 3) Pre and Post-operative nutritional supplements 4) Post-operative oral nutritional supplements Results:No differences in outcome in terms of major complications, anthropometrics and Q-o-l, complications and was deemed to be cost-effective.
Soop [529]	N=18.Patients were randomised to receive either immediate post-operative enteral nutrition or for the first 3 days. Study focused on insulin resistance and post-operative nitrogen balance. C nitrogen balance and does not increase hyperglycaemia when compared to hypocaloric feeds.
Stewart [415]	N=88 undergoing elective colorectal resection with anastomosis. Patients were randomised to post-op or nil by mouth (N=40) until passage of flatus or bowel motions. The patients in each group were well matched for age, sex and type and duration of surgery. T tolerated a diet, passed flatus, used their bowels and were discharged home 2 days sooner (9
Torosian [471]	Critical analysis of perioperative nutrition support for patients undergoing gastrointestinal surge parenteral nutrition both pre and post operatively. Four post op enteral nutrition trials were ana individual studies are not confirmed when analysing combined data from all studies; it revealed morbidity or mortality rates.
Velez [68]	A multicentre pilot cohort study in patients undergoing GI surgery with intestinal anastomosis. N failed to meet the inclusion criteria due to mechanical tube issues. EN was commenced in 46 patients within 24 hours. Feed type was a peptide based feed (*Pept* well tolerated in the majority of surgical patients with a low incidence of complications and side

	faster resolving of bowel function which may shorter LOHS.
Zapas [517]	Carried out a benefit/risk analysis of prophylactic jejunostomy comparing complication rates, a N=92. Concluded that benefit/risk ratio is low mainly for the significant rate of complications related to

1.6.8.4 Cost Effectiveness comparison of enteral nutrition versus standard management

Very few RCTs have been designed to compare the economic costs of using EN versus STD hospital management post-operatively. However, cost comparisons have been made several studies. These will be presented in this section.

A study from the USA by Hedberg *et al* (1999) [530] concluded that EN delivered via a needle catheter jejunostomy within 12 hours of major surgery (as compared to standard care) led to a cost saving of $4,450 per patient in the early EN group in patients post major GIT resection, as compared to STD care.

Beier-Holgerson and Boesby (1996) [12] demonstrated that the cost of providing EN to patients undergoing major resection for GI cancer could deliver a potential cost saving of 50%; £1000 for EN patients and £2000 for STD patients, the costs were based on the differences in LOHS. This was reiterated by Carr *et al* 1996 [13] who too surmised that the use of post-operative EN could lead to cost savings.

A systematic review and meta-analysis of the RCTs comparing any method and type of enteral feeding started after surgery with nil by mouth and standard management in elective gastrointestinal surgery was conducted in 2001[17]. The authors concluded that early feeding was associated with a shorter length of hospital stay and reduced frequency of infections, the greatest reduction being in wound infections. They also surmised that cost savings could be achieved.

While the RCTs included were heterogeneous in clinical terms, the effect of early nutrition seemed to be homogenous. The authors conclude that there is little evidence that keeping patients 'nil by mouth' is beneficial. However, they recommended that an adequately powered RCT addressing the flaws and limitations in the RCTs to date should be conducted.

1.6.9 Immuno-enhanced Enteral Nutrition

Most of the studies examining EN in postoperative patients have used standard enteral formulas. Recently, more studies have used formulas, with immune enhancing properties.

To date there has been 7 RCTs [291, 489, 507, 531-534] exploring this subject. Several studies have indicated that immuno-enhanced enteral nutrition was superior to enteral nutrition in lowering incidence of infections and complications. Daly *et al* (1995) [531] examined a formula supplemented with arginine, RNA, and omega-3 fatty acids in patients with upper GI malignancies. Eighty-five patients were randomised to receive either a supplemented enteral formula or a standard enteral formula. Both groups had a similar calorie intake but nitrogen intake was significantly greater in the supplemented group. A lower incidence of infectious and wound complications was found in the supplemented group (11% vs. 37%) and length of stay was shorter. There was no control arm in the study that did not receive nutritional support in the study design.

McCarter *et al* (1997) [489] conducted a prospective study of 167 patients undergoing upper GI surgery for carcinoma of the oesophagus, stomach and pancreas. Patients received a standard or supplemented formula via a jejunostomy postoperatively. The authors did not examine the occurrence of complications in the two groups but instead examined the tolerance of the enteral feeds. The majority of symptoms experienced were mild and included abdominal cramping, abdominal distension, nausea and diarrhoea. This is not attributed to the use of different formulas as no significant difference was found in tolerance of feed between the standard and immune enhanced formula group. The direct correlation between jejunal feeding and the occurrence of symptoms is not clear once again due to the absence of a control group without an enteral feed.

Braga *et al* (1998) [55] used an immune enhancing formula in 166 patients who underwent abdominal surgery for gastric or pancreatic cancer. Patients were randomised to TPN, standard enteral feeding or enteral feeding with the enriched formula. Greater than 10% weight loss in the preceding 6 months occurred in 78 patients. There was a trend towards fewer infections in the EN group; it did not reach statistical significance, and the severity of infection was lower with the enhanced formula than with the TPN or standard enteral formula.

A study by Senkal *et al* (1999) [507] focused on providing immuno-nutrition to malnourished surgical patients. The authors found that immuno-nutrition given in the pre-operative period alone or in the pre and post-operative period improved clinical outcome and shortened hospital stay, when compared to standard enteral nutrition.

A series of more recent studies from Italy [291, 532-534] have provided more evidence of the benefits of perioperative enteral feeding. Preoperative oral feeding with an immune enhancing formula combined with postoperative jejunal feeding with the same formula in patients with GI cancer resulted in a significantly reduced incidence of postoperative infectious complications [532, 533]. Further studies were then conducted in malnourished and well-nourished patients. In malnourished patients the greatest benefit on the reduction of complications was achieved with an immune enhancing formula given peri-operatively [532]. In well-nourished patients the provision of an immune enhancing formula preoperatively alone was sufficient to significantly reduce infectious complications and length of postoperative stay [291].

A consensus from the USA recommended that patients undergoing major elective GI surgery who were malnourished should receive early enteral nutrition using immune enhancing nutritional support. In a meta-analysis of 27 studies [535] immuno-nutrition was associated with a reduction in infectious complications, but no effect on mortality was demonstrated.

One concern of these studies is that few opted for a control group using standard management alone. Most of the RCTs in which immunonutrition formulas were used have compared it with standard enteral nutrition. What is important, clinically, is how enteral feeding *per se* impacts on clinical outcome and LOHS. Following a detailed review of the literature this still remains a contentious issue.

1.6.10 Pre-operative Enteral Nutrition

Pre-operative EN in patients with gastrointestinal cancer has been evaluated in two RCTs [368] [279], both showing a benefit from using pre-operative enteral nutrition in improving clinical outcome post-operatively. In the study [368] pre-operative enteral nutrition given orally significantly reduced post-operative complications from 30 % to 10 % when compared to standard hospital diet.

The enhanced recovery after surgery programme (ERAS) [536] has been widely studied. The optimising of nutrition support peri-operatively along with early-enforced mobilisation, adequate analgesia forms the basis of this programme. The evidence comes from colorectal surgery and has not as yet been evaluated in UGIT surgery. The ESPEN working group [537] provides a detailed review of this evidence to support this programme.

1.6.11 Limitations with Clinical Trials in Nutritional Support in Surgical Patients

The reasons why previous studies remain inconclusive as to which is the optimal modality of managing patients post-operatively could be due to one of three factors:

1. The delivery of peri-operative nutritional support does not improve clinical outcome in any patients.

2. Peri-operative nutritional support does not improve clinical outcome in the patients studied to date.

3. Peri-operative nutritional support does improve clinical outcome but previous clinical trials have failed to demonstrate this. This could be secondary to the fact that previous studies were not designed to evaluate the efficacy in reducing complications.

The next section will discuss potential limitations in the trials to date.

Location of jejunal catheter in small bowel

It appears from reviewing the literature that many authors fail to highlight the exact location of the tube in the intestines. Smith *et al* (1985) [358] recommended placing the jejunal catheter at 70cms distal to the DJ flexture to prevent reflux of feeds into the proximal small bowel.

Position of the tube in the small bowel is essential for maximizing the absorption of nutrients. Also placing the jejunal catheter too distal or too proximal in the small bowel may lead to problems. Too distal may lead to proximal small bowel atrophy and hence translocation. Too proximal may lead to the reflux of feed, causing increased pressure on the newly formed anastomosis.

Time of Commencement of Enteral Nutrition

Many studies had varying commencement times for nutritional support post-operatively. Some studies commence enteral nutrition immediately after the patient returned from the operating theatre [12, 13]. Some started within 24 hours [16, 503, 521], some commenced within 24-48 hours [357] and one

commenced after 3 days [358]. In one paper it was actually unclear when EN was commenced. In comparison to the PN studies which all commenced PN within 24 hours of the patients returning from the operating theatre.

One study by Neumayer *et al* (2001)[538] summarised the important issues and concluded that for EN to be beneficial it needs to be both early (within 12 hours) and in sufficient rate and volumes. The authors of this research concluded this might be the reason why many trials do not show a difference between EEN and STD management.

Type of feeding used

In EN studies there is are wide variation in the types of EN used. There are many different commercial brands available; these can be categorized into whole protein, semi-elemental (pre-digested), elemental, disease specific and immuno-nutrition feeds. It is not clear from many studies, which type of feed was used, and whether the authors 'tailored' the feed type to the patient needs. Failure to 'tailor' the feed type to the patient could predispose to increased development of complications.

Pre-operative nutritional status

It is clear from the literature that malnutrition predisposes an individual to alterations in physiological, psychological function and immune function as outlined in sections 1.4.2-1.4.4. It is essential that clinical trials studying peri-operative nutrition have the same BMI and mean percentage body weight loss at baseline to ensure comparability of the randomised groups. It may be that malnourished patients respond better to nutritional support than 'at risk' or marginally malnourished patients [539].

1.6.12 Consensus of Clinical Trials and Meta-analysis to date

Several national clinical guidelines on nutritional support have been published in different countries [537, 540]. These guidelines agree on many key elements, primarily if the GIT is functioning and the patients are high risk of malnutrition or are malnourished then EN should be used. Importantly, they all suggest that to date, the evidence is not adequately robust to provide a radical change in post-operative practice. The meta-analyses

1.6.13 Summary of Section

This section has provided a robust literature review of the modalities available for the provision of nutrition to surgical patients; these include the use of parenteral or enteral nutrition, both of which have different physiological effects. The evidence to support their efficacy and effectiveness in the peri-operative management of surgical patients remains inconclusive.

1.7 The Design of Clinical Trials

1.7.0 Introduction

Previous clinical trials of post-operative nutritional support (either enteral or parenteral) have fairly consistently demonstrated that nutritional support is superior to traditional, standard management i.e. nil by mouth with no nutritional support in maintaining nutritional status; namely measures of nutritional intake [12, 16, 18, 357, 360, 361], weight [13-16, 18, 354-358], nitrogen balance [378, 379] and improved muscle strength and function [16, 361, 368] [13, 14].

Whilst improvement in nutritional status *per se* is a legitimate secondary goal of treatment it can hardly justify the substantial time and expense required providing these therapies, therefore it is imperative that trials study the effect on clinical outcome.

Section 1.6 provided a consensus view, that the use of nutritional support in surgical patients undergoing major UGI resection is not proven to be clinically beneficial in terms of optimising operative outcome and survival.

The necessity for evidence-based medicine over recent decades has meant there is a need for healthcare treatments to be examined for their efficacy. The efficacy of an intervention describes the therapeutic effect of the intervention under ideal circumstances. Effectiveness describes the benefit of an intervention compared with other interventions in routine clinical practice and efficiency is the benefit of an intervention compared to the resources it consumes.

So often in clinical nutrition trials, the nutritional intervention is tried on patients to determine its effect. These trials do not have a comparison group and are typically observational and uncontrolled [541].

The Randomised Controlled Trial (RCT) is considered the 'gold standard' comparative study design for evaluating the efficacy, the efficiency and the effectiveness of different healthcare interventions [542, 543].

A RCT has a minimum of two comparable groups. These groups are accurately assessed with regards to the outcome or effects of a new or existing intervention

(the experimental variable). Typically, there is a comparison of the group receiving the 'experimental' intervention and the group receiving standard or conventional treatment. This group is often termed the control group.

RCTs are often considered one of the best ways of delivering clinically relevant results that can be extrapolated into clinical practice. The process of randomisation reduces selection bias which is considered to be the main source of bias in clinical research [544]. RCTs have been advocated by Verhagen *et al* (2001) [545] who suggested that RCTs increase the likelihood of the trial to generate unbiased results that are sufficiently precise and allow application in clinical practice.

There are limitations with RCTs, however, which are listed below:

1. In a RCT the results and data collected from the study sample are used to make inferences about the population of all such subjects. Thus, it is essential that the study sample adequately represent the population who would normally receive the treatment. Too restrictive eligibility criteria for inclusion in a trial may make the results difficult to extrapolate to the population. In addition, an unrepresentative sample may result from clinicians restricting which patients put forward to enter the study.

2. The trial setting may be atypical from that of usual clinical practice. The setting should be typical of the clinical environment and setting where the procedures and treatments are usually conducted.

3. There may be professional resistance to the concept, hypothesis and implementation of the study. Some clinicians may be unwilling to refer their patients into the study. Using restrictive eligibility criteria means the results are less generalisable. Some clinical staff may assume it is unethical to deny any

patients the treatment because it is 'believed' by them to be better than 'standard' treatment.

4. Trials, which have a small number of eligible subjects in the study population, may make a trial unethical in terms of the long and expensive period of the trial. The use of Multicentred trials may be advantageous, leading to an improved accrual rate. They have the advantage that patient accrual is quicker and the intended size is reached more quickly. The end result should be that a multi-centre trial reaches more reliable conclusions at a faster rate so that overall progress in the treatment of a disease is enhanced. By involving patients from several centres, any conclusions have a broader more representative base than can be reached in a single centre.

However, multi-centred RCTs have been criticised. The conduct of multi-centre trials involves complex administration and planning; they are expensive to run and therefore adequate funding is required. Seamless communication between the research team and clinical staff across the centres is essential. There may be fundamental differences in baseline care of the patients with differing outcomes. Therefore standardisation of intervention and education and training of clinical staff of trial procedures is paramount. The use of stratification based on each hospital centre can alleviate some of these problems and will be discussed later in this chapter.

5. Patient preference. Some patients may have a preconceived idea of what treatment option is likely to benefit them and therefore may demonstrate a preference leading to non-compliance of the treatment allocated. This may lead to the results being biased. Zelen's design [546] aims to address these issues. Patients are randomised before they consent to take part in the clinical trial. Two types of the design exist: double and single consent. In the double consent version patients are initially offered the treatment to which they were randomised; however, if they decline the randomised treatment, they can then be offered

alternative therapies including the experimental treatment. In the single consent version only patients offered the experimental treatment are told there is an alternative treatment (the control) available. Patients randomised to the control treatment are not allowed the experimental treatment (although they are given unhindered access to any usual treatment facilities). Analysis is undertaken with patients retaining their original assignment. There are reported problems with this design [546]. There is a view that these studies are unethical, introduce bias and require more subjects to be included in the study.

1.7.1 Contrasting Explanatory with Pragmatic Randomised Clinical Trials

There are two main types of RCTs [547]. Explanatory RCTs examine efficacy and pragmatic RCTs examine effectiveness. The next section will outline the contrasting principles differentiating these two types of trial.

1.7.1.1 Explanatory trials

These trials test scientific hypotheses. They examine the therapeutic benefit of a particular treatment. There is a strict protocol, with strict inclusion and exclusion criteria. These trials often have a placebo.

Outcomes are usually intermediate and based on the physiological and molecular origin of the intervention treatment. In view of these non clinical outcomes, there is doubt as to how well the results of these trials can be incorporated into clinical practice [547] [548].

1.7.1.2 Pragmatic trials

These trials tend to closely mimic typical clinical practice. They aim to examine the effectiveness of two interventions in clinical care. Instead of a placebo the control group receives usual care or standard care commonly used for that condition. Blinded allocation is usually not possible.

Eligibility criteria should be used with minimal exclusion criteria to produce a heterogeneous representative group of subjects. Clinician and patient biases are not viewed as detrimental but accepted as part of the response to treatment. It is accepted that both treatment and control groups have placebo effects, which may be of differing magnitude. The treatment effect is taken as the difference between the two treatments reflecting the likely clinical response.

A primary outcome measure is used. This is supplemented with the use of secondary outcome measures, which are based on a wide range of assessments. The inclusion of a cost analysis and a report of health related quality of life are typical [549]. Results are usually reported on an intention-to-treat-basis [547, 548]. The RCT described in this thesis is a pragmatic trial.

1.7.2 Choice of intervention and Control Groups

For the trial to be ethical there must be clinical equipoise as to which is the optimum treatment before the trial commences. There must be doubt as to which arm of the study is superior, based on a critical review of existing literature.

In theory, the random allocation of patients to one of two groups should not disadvantage patients if true equipoise exists. However, true equipoise is affected by past experience, observational studies, from previous underpowered studies.

1.7.3 Sample Size and Power Calculation

Many RCTs identified in the review of the literature (chapter 1.6) have small sample sizes and often do not report the power calculation in their method section. The use of a power calculation provides a scientific basis for the number of subjects required to make up the sample size that is needed to reject the null hypothesis with a given level of confidence (usually 80%).

RCTs should be sufficiently large to demonstrate a high probability of obtaining a significant difference between the randomisation groups where real differences exists. Sample size calculations should always be reported [550].

1.7.4 Randomisation

The selection of the randomisation groups is a primary factor in the design of a RCT [551]. Randomisation refers to the random allocation of the intervention group or 'arm' of the study to which the patient is to be distributed. It should be conducted in a way that each subject has an equal chance of being allocated to either group. Random allocation aims to reduce selection bias, by reducing the effects of extraneous variables. The reduction of extraneous variables increases the probability that the differences observed between the randomised groups, is due to the intervention. Pocock (1983) outlined the three main components of randomisation:

1) The generation of the random sequence

2) The concealment of the treatment allocation

3) Stratification

Pocock (1983) [552].

These will be discussed in turn in the next section.

1.7.4.1 Generation of the Random Sequence

There are several methods of preparing a list of random allocation to treatment. The key issue is that whichever method is used it should be reported and reproducible [550, 551].

Simple randomisation results in every participant in the study having the same chance of receiving either treatment option. The sequence can be generated using a random number table or computer-generated series of numbers [553]. The benefit of simple randomisation is that each treatment assignment is completely unpredictable. However, there is a chance that treatment allocation may be unequal, resulting in unequal randomisation group sizes.

Block randomisation ensures exactly equal treatment numbers are used at certain equally spaced points in the sequence of treatment assignment. To reduce again the issue of prediction of the sequence the blocks are usually

reasonably large [552]. The method used for the current study was block randomisation.

1.7.4.2 Concealment of Treatment Allocation

This is a very important aspect of randomisation. If the allocation of the next patient is known in advance then this may affect the decision to enter that patient into the trial. Failure to adequately conceal the treatment allocation can lead to selection bias. A systematic review by Chalmers (1983) [554] reported that inadequate concealment lead to an exaggerated odds ratio of treatment effects by 30-40%.

The use of sealed opaque envelopes is commonly used but has been criticised as being inadequately secure [555]. Many large commercially funded trials use an independent third party preferably via telephone [550]. However this is often not practical for small budget clinical trials.

1.7.4.3 Stratification

In any RCT, the aim is to have treatments groups that are similar with regard to baseline patient characteristics. This is especially so for prognostic factors. The literature review is essential to determine these factors and these should be known prior to commencing the RCT.

Stratification allows the sample population to be separated into stratification groups or stratum, based on these factors. This ensures balanced allocation of important prognostic factors aiming to increase the sample's precision. There are however disadvantages of using stratification. Stratification introduces increased complexity into the randomisation process potentially increasing the chance of errors. There may also be an uneven distribution of subjects across the stratum, resulting in an imbalance of subjects per treatment groups [552].

In multi-centre RCTs stratification is usually based on each hospital centre. This takes into account the differing healthcare delivery systems that may be present in each centre. For the purpose of this RCT, this was the only strata used. This is because if the number of strata increased, to stratify for a prognostic factor, this

would have increased the number of patients to power the trial, ultimately increasing the duration of the trial. This would have had implications for funding.

1.7.5 Blinding

Blinding is separate from and should not be confused with allocation concealment. The theory behind blinding is that if a patient in a clinical trial is aware that he or she is in the treatment group there may be a psychological benefit affecting their response. The reverse may be true if the patient knows they are receiving standard care. The research team may also introduce bias; if they are aware of the treatment allocation they may often unintentionally follow up these patients more closely.

To reduce bias and if blinding was not possible in the intervention stage then blinding can occur at the data analysis stage. Blinding the statistician conducting the statistical analysis reduces potential bias.

1.7.6 Ethical Issues

A RCT is an experiment on human beings [541]. Therefore, there are several important ethical issues relating to the design and implementation of clinical trials. The ethical principle governing research is that patients should not be harmed as a result of participating in the research trial [556].

The dignity, rights, safety and well being of participants in a research trial must be of primary consideration [445]. The ethical committee provides independent expert opinion on whether the proposed research is ethical and respects the dignity, rights, safety and well being of participants.

1.7.7 Frameworks for Conducting Clinical Trials

There are several frameworks, which provide guidance for the development and evaluation of complex interventions to improve heath, within the framework of a Randomised Controlled Trial (RCT). These will be discussed in the following section.

1.7.7.1 The Research Governance Framework

In 2002, The Research Governance Framework was published by the Department of Health [557]. Prior to this, the Medical Research Council (2000) [542] was the framework on which most UK clinical trials were based.

The Governance of NHS research aims to provide the public and key stakeholders with the confidence that high quality research will be conducted [557].

The Research Governance Framework outlines the key elements of a quality research trial to be:

1. That all participants in the clinical trial should be treated with respect. They should be treated with dignity, have their rights, safety and well-being considered to be the highest priority at all times during the conduct and follow up of the trial.

2. The development of the clinical trial must value the diversity within society, and consider this in the development and conduct of the clinical trial.

3. The Principal Investigator (PI) and the research team must demonstrate both personal and scientific integrity, during the conception and conduct of the trial.

4. The PI must be able to demonstrate strong leadership and be accountable for the delivery of the trial.

5. The organisation where the research is conducted must be able to provide clear and supportive management to the PI and the research team. This is typically the role of the Trust or organisation Research and Development Committee.

1.7.7.2 CONSORT (Consolidated Standards of Reporting Trials) Guidelines

The CONSORT guidelines were developed to improve the reporting of clinical trials. Traditionally the reporting of clinical trials has been criticised [558, 559]. As a result, published and accepted standards, CONSORT, were developed to ensure the quality of reporting of RCTs [560]. Further updates have been more recently published [558, 559].

1.7.7.3 The Role of Clinical Research Guidelines in the United Kingdom

As discussed RCTs provide the best way of comparing the efficacy and effectiveness of different healthcare interventions, however this is only applicable if reporting is to a high standard. Readers should not have to infer what was probably done, they should be told explicitly. Robust methodology should be used and reported comprehensively. It seems reasonable to hope that, in addition to improved reporting, the wide adoption of these guidelines will improve the conduct of future research by increasing awareness of the requirements for a high quality study. The aim of the CONSORT statement means that the authors of clinical trials will have to report details of research methodology emphasizing the importance of adequately reporting the randomisation process [561]. The guidelines have been specifically developed to encourage transparency and reporting the methodology of clinical trials. The use of these guidelines will assist the investigators in the reporting of clinical trials. By using the CONSORT standards and flowchart for reporting clinical trials the authors will provide adequate data and information to allow the readers to decide if the study design was robust and sufficient to change their local clinical practice by incorporating the evidence into local policy and procedures.

1.7.8 Summary of Section

This section has discussed the importance of RCTs in evaluating the efficacy, efficiency and effectiveness of differing healthcare interventions. It has outlined the benefits of using a pragmatic design in clinical trials, as they tend to closely mimic clinical practice. However, the limitations of RCTs were also outlined.

What is apparent is that they are several key aspects that need to be considered and implemented in order to produce high quality, robust clinical trials. These include the importance of an adequate sample size, rigorous randomisation techniques, the importance of concealment of treatment allocation, the use of stratification and blinding and their limitations. It also outlined the important ethical considerations that are required when conducting clinical trials.

This section ended with an outline of the two main frameworks used in the running and reporting of clinical trials. These are the research governance framework and the CONSORT (Consolidated Standards of Reporting Trials). These are essential frameworks in which to adhere to ensure excellent quality clinical trials.

2. Original Work: A Randomised Controlled Trial of Early Enteral Nutrition versus Standard Management in patients undergoing Major Upper Gastrointestinal Resection for Malignancy

2.1 Methods of the Main Study

2.1.0 Introduction

The need for the current study was apparent after recognition that post-operative nutritional practices were *ad hoc* in hospitals around the United Kingdom [59, 220]. These practices involved the traditional practice of starvation with 'nil by mouth', parenteral and/or enteral nutrition. To date, the clinical evidence remains inconclusive as to which is the optimal post-operative management.

This chapter will present the aims, objectives and detail the choice of clinical outcomes and methods used for the RCT described in this thesis.

2.1.1 Aim of the Trial

The aim of the RCT was to compare the use of post-operative early enteral nutrition (EEN) delivered via a needle catheter jejunostomy with traditional, standard management (STD). Comparisons will be defined by measuring the length of hospital stay, the clinical outcome, the HRQoL and by differences in cost in patients undergoing major upper gastrointestinal resection for malignancy.

2.1.2 Primary (null) Hypothesis

Patients who receive early enteral nutrition (within 12 hours of leaving the operating theatre) compared to patients who receive standard management have no differences in their length of hospital stay.

2.1.3 Primary Objective

To determine the difference in length of hospital stay (LOHS), between the two randomised groups.

2.1.4 Secondary Objectives

1. To determine if there was any difference in the development of major complications between the two groups.

2. To determine if there were any differences in readmission rates between discharge and 6 weeks and between 6 weeks and 12 weeks after discharge.

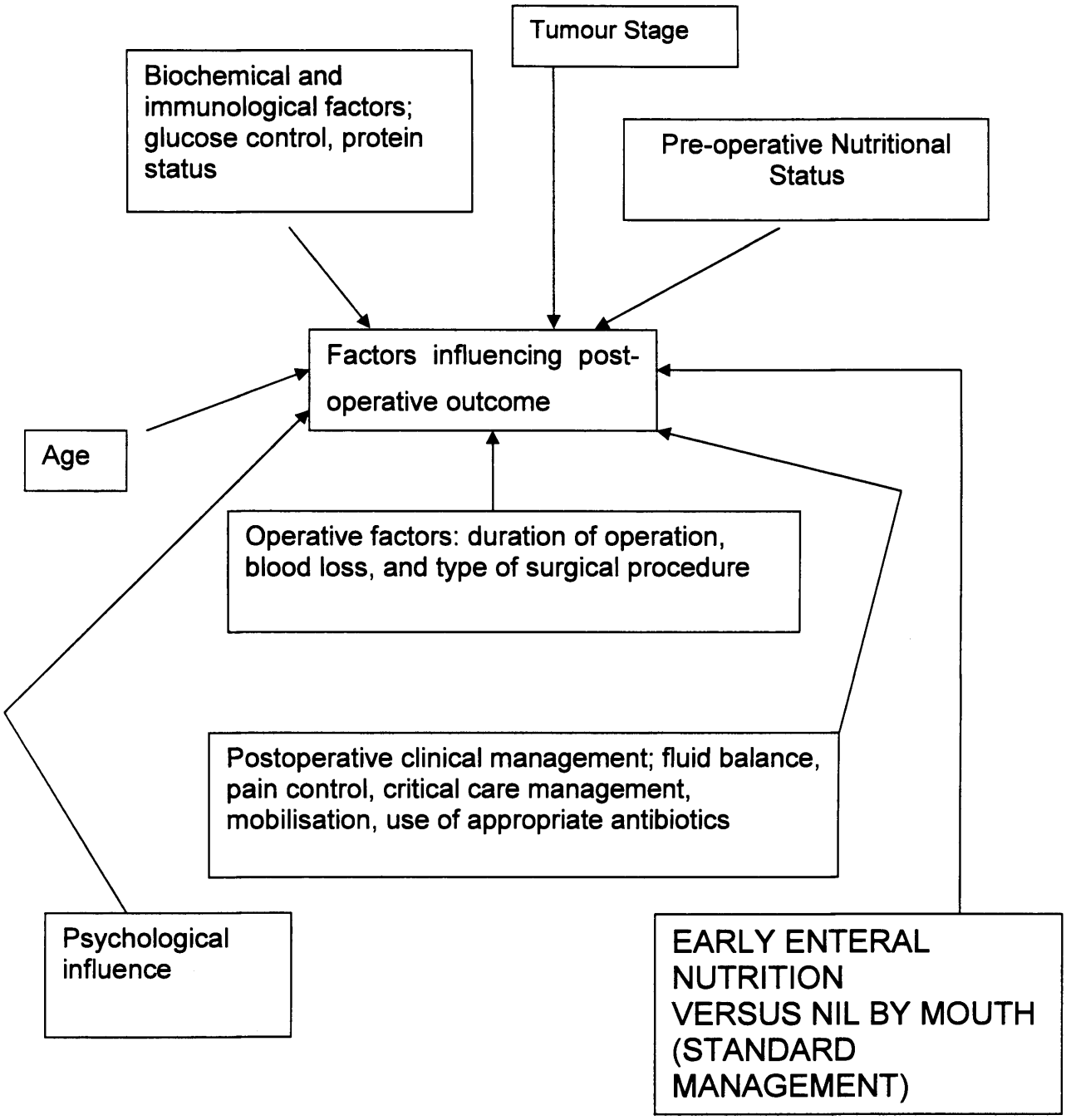
3. To examine the feasibility of EEN following major gastrointestinal surgery for malignancy.

4. To determine if there were any differences in nutritional outcome, for the two groups.

5. To report any differences in health related quality of life for the two groups 12 weeks post operatively.

6. To estimate any differences in costs between the two groups

2.1.5 Conceptual Map



2.1.6 Choice of Clinical Outcomes

Prescott (1999) [550] suggested that it is beneficial to choose a primary outcome indicator and supplement this with a limited number of secondary outcomes, as was the case in the current RCT. Other alternatives in clinical pragmatic trial design can be to use a combination of multiple outcomes or endpoints to determine the efficacy and efficiency of the proposed interventions. The use of multiple endpoints can lead to Type I error due to over analysis of the data. The Bonferroni method [541] aims to adjust the statistical significance according to the number of tests performed on the same data set. However, this method has been criticised to be too conservative leading to Type II error. Pernerger *et al* (1998) [562] suggested that in order to avoid either a Type I or Type II error, the author should detail what statistical methods were used and discuss the interpretations of each results, allowing conclusions to be reached without the use of Bonferroni methods. This section will provide the justification for the choice of outcome made in this RCT.

2.1.6.1 The Primary Outcome- Length of Hospital Stay

Studying clinical outcomes is an important aspect of evaluating healthcare delivery. One outcome measure used in clinical trials is LOHS [563]. Length of hospital stay was selected as the primary outcome for the current RCT, to allow comparison with the previous enteral nutrition RCTs [12] [13, 503] and in a meta-analysis [17] which have also used length of hospital stay.

To date there is no agreed definition of LOHS. Length of hospital stay has been defined as:

> *"The time from the date of the index operation to the date of discharge whether home, the transfer to a subacute service or death which ever comes first"*

Collins *et al* (1999) [564] page 255

However, LOHS can be affected by many factors, including pre-operative age, physical status score, intra-operative factors such as blood loss, and duration of time in theatre, type of surgical procedure and the presence of co-morbidities. These factors have all been associated with prolonged LOHS [565, 566]. Post-

operatively the development of major complications have also been correlated with prolonged LOHS [564]. In addition, social factors including patients waiting for transfer to convalescence healthcare organisations can also prolong LOHS. It was for this reason that for the purpose of this study LOHS was defined as:

The time from the day of the index operation to the date the operating surgeon decides the patients is medical fit for discharge

This definition takes into account any administrative factors that may prolong discharge for example waiting for social support packages. Similarly, LOHS can be subjective if robust criteria are not used to determine when patients are medically fit for discharge. For the purpose of this RCT the following discharge criteria was used to decide whether the patient was ready for discharge home.

Patient must be able to:

1. Get out of bed and mobilise
2. Prepare a drink or food.
3. Get to the lavatory in their home

Taking all this in this confounding factors into account, LOHS was still considered to be the most appropriate primary endpoint, for true comparison with the previous literature.

The use of LOHS as a primary outcome measure can be criticised if subjects are discharged back into the community with complications. Information on the number of hospital readmissions is essential to support the result of the differences in length of hospital stay. Data was for readmissions for all patients in the current RCT, between discharge and 6 weeks and 6 and 12 weeks post-discharge.

2.1.6.2 Secondary Outcomes

The Development of Major Complications

The development of major surgical complications can prolong length of hospital stay. Therefore the measurement of the occurrence of major complications is crucial. Surgical complications are associated with increased hospital costs and a reduction in a patient's quality of life [564]. It is for this reason that healthcare organisations are focused on reducing the development of major and minor complications [564].

For the purpose of this study post-operative complications, both infective and non-infective, were diagnosed by nursing, surgical or critical care staff that were not directly involved with the trial. Consistency was ensured by clear definition of the major complications as outlined in table 2.2.1.

These definitions were based on the definitions used in a previous large clinical nutrition RCT [338]. In addition, the definitions were adapted to provide a consensus following discussion with Surgical and Critical Care colleagues.

Table 2.2.1 The Classification of in Hospital Major Complications

Type of Complications	**Signs of Symptoms of the presence of the Complications**
Wound infection	Any redness or tenderness of the surgical wound with a discharge of pus.
Abdominal Abscess	Deep collection of pus located in the abdominal cavity.
Chest Infection	Abnormal Chest X-Ray with pyrexia (>38 °C.) and WCC > 12000 cells/ul +/- positive sputum.
Urinary Tract Infection	$>10^7$ Micro-organism/ml of urine.
Septicaemia	Two consecutive +ve blood cultures.
Open Abdominal Wound	Surgical Wound gaping >3cm.
Post-operative Bleeding	The Need for blood transfusion > 2 units.
Anastomotic Leak	Any dehiscence of an anastomosis with clinical & radiological evidence
Respiratory Failure	Presence of dysnopnea and respiratory rate >35/min or Pa O_2 <70mmHg on air.
Circulatory Insufficiency	Unstable blood pressure requiring use of extra fluids &/ or inotropes.
Renal Dysfunction	Necessary haemodialysis/ filtration.
Hepatic dysfunction	Increased serum bilirubin (50% above baseline).
Pancreatic Fistula	Daily output of fluid >10mls from surgical drain with amylase content 5 times higher than serum.
Delayed Gastric Emptying	The need for gastric decompression for 8 days, or more post-op.
Multi-Organ Failure	Two, or more, organ failures.
Systemic Sepsis	Presence of Systemic Inflammatory Response Syndrome.
Deep vein thrombosis	The development of a blood clot or thrombus within the vascular system confirmed by a Doppler Scan.
Pulmonary Embolism	Presence of a thrombus in the pleural cavity diagnosed with a VQ scan or angiogram.
Cerebro-vascular accident	The development of embolic, thrombotic or haemorrhagic vascular accident or stroke persistent for more than 24 hours
Return to theatre	Return to theatre within 30days of the index operation.
Pleural Effusion	The presence of fluid between the pleura and the chest cavity and lining of the lungs.

Complication Ratios

A study by McAleese and Oldling-Smee (1994) [567] described the impact of major complications on length of hospital stay. The authors developed a calculation termed the 'complication ratio'. This ratio is the factor that LOHS (in days) will be increased if a patient develops a complication compared with a patient who develops no complication. It is calculated using the following:

$$\text{Complication ratio} = \frac{\text{Average LOHS (in days) with a particular complications}}{\text{Average LOHS (in days) without that complication}}$$

According to this study [567] surgical complications in general increased a patient's average length of hospital stay by a factor of between 3.3 and 4.4 times the routine inpatient period. For example if routine stay is 5 days and a patient develops a major complication then LOHS will be 16.5-22 days. The authors concluded that respiratory tract and wound infections were most likely to prolong LOHS. In addition, the authors isolated age as the most predictive variable with an age 60-69 years having the largest impact on development of complications.

Table 2.2.2 Complication Ratios for Key Surgical Procedures (McAleese and Oldling-Smee (1994)[567]

Type of Complication	Complication ratio
All major complications	3.3-4.4
Infectious Complications	
Wound Infection	2.43
Chest Infection	1.99
Non Infectious complications	
Delayed gastric Emptying	3.4
Pleural effusion	1.99
Chylothorax	NA
Anastomotic Leak	3.4
Abdominal dehiscence	1.85
Respiratory Failure	1.99

The complication ratios for infective and non-infective major complications were calculated for this RCT.

The Development of Minor Complications

The presence of the following was recorded daily post-operatively, from the nursing and medical records. In addition the patient was asked to report and confirm the symptoms.

1) **Nausea** was defined as "the feeling that one is about to vomit" [568].

Patients were asked to report if they had complained of nausea in the previous 24 hours. Any report was taken as confirmation of this symptom. However, the use of nausea is a subjective measurement. It is, however, an important clinical outcome indicator in post-operative patients [64, 65, 69]. For this RCT, the presence of nausea in the first post-operative week was considered important for comparison between the two randomised groups.

2) **Vomiting** was defined as "the reflex action of ejecting the contents of the stomach through the mouth" [568].

The actual volume of vomit was recorded from the nursing records in millilitres per day. The total volume was recorded per 24 hours; the presence of vomiting in the first post-operative week was used as an endpoint.

3) Abdominal distension.

The development of abdominal distension has been reported in several other RCTs. Patients were asked if they were complaining of abdominal cramping or distension. In addition, if the surgical team had documented in the medical records that the patient had reported these symptoms this was recorded in the trial documents.

4) **Nasogastric Aspirates**. This was defined as the volume of gastric or intestinal secretions that were withdrawn by aspiration of the nasogastric or gastrostomy tube per 24 hours

5) **Pain Score**. This was recorded from the nursing records. The visual descriptive scale was used [569]. The rankings were categorised into mild, moderate or severe.

6) Bowel function. The following was the definition used to define bowel function for the purpose of this RCT.

Passage of flatus was defined as the patient reporting the passage of gas per rectum. The day this first occurred was recorded.

Passage of stool was defined as "the defaecation and evacuation of the bowels" [568].

Diarrhoea was defined "as the passage of loose or watery stools more frequently than 3 times per day" [568].

Ultrasound imaging of Gastrointestinal Motility

The use of ultrasound imaging (USS) was used to quantify the frequency of small bowel peristaltic waves. The principal investigator and a Senior Surgical Colleague performed the USS.

Methods

1. The USS imaging was performed on Day 1-2, and day 5-6 post-operatively.
2. The USS probe was placed on the patients' abdomen in the left iliac fossa avoiding the surgical incision and wound.
3. The probe was held with moderate pressure.
4. The number of peristaltic waves per minute was counted on the screen and recorded.
5. In addition bowel sounds were quantified using auscultation. The following was recorded:
    a. Absent
    b. Sluggish
    c. Normal

d. Hyperactive

A member of the Surgical Team repeated this stage.

Fluid balance

Fluid balance has an important effect on clinical outcome and has been shown to increase the development of post-operative complications [570] [399]. Fluid loss and administration of intravenous fluid were recorded from the day of the operation, until day 9 post-operatively.

The fluid balance data was recorded from the patients nursing records. The nurse in charge of the patient completed all records every 12 hours on the ward and every hour on critical care units. The loss of fluid in the urine, drains, nasogastric aspirates, vomit and any faecal fluid was recorded as fluid output.

Fluid input was recorded as the volume of intravenous fluid, enteral feed and intravenous and enteral drug volume. All measurements were measured in millilitres.

The development of oedema was recorded as an important clinical outcome indicator. Oedema was defined as, "The presence of excessive amounts of fluid in the intercellular tissue spaces of the body, due to increased transudation of fluid from the capillaries." [571].

The presence of oedema was determined by palpating the peripheries with a thumb. Oedema was recorded if an indentation remained when the thumb was removed after 5 seconds.

The Delivery of Early Enteral Nutrition

Several previous observational studies have suggested that enteral nutrition is safe and well tolerated in the post-operative phase [64, 65, 69]. Many of these trials were retrospective. This RCT aimed to collect data prospectively on the delivery of enteral nutrition.

Complications with the Needle Catheter Jejunostomy

The presence of complications associated with the needle catheter jejunostomy was recorded daily during hospital admission. Complications such as catheter dislodgement, catheter blockage and catheter entry site infection were recorded. Other major and minor complications attributed to the jejunostomy which were documented in the medical notes, were also recorded.

The Volume of Enteral Nutrition

The volume and rate in millilitres per hour of enteral feed delivered each day was recorded from the nursing records. This was calculated on a daily basis as a percentage of nutritional requirements [572].

The number of patients who had their enteral feed stopped for more than 12 hours was also recorded together with the reason why the feed was stopped.

Nutritional Outcomes

The following indices of nutritional status were chosen on the basis that they are objective, minimally invasive and easy to obtain [184].

There are many limitations associated with anthropometry (i.e. measurement) in clinical practice. These relate to the accuracy, reliability and sensitivity of the measurement. This section will outline the methods used to measure the nutritional parameters and will then present the measurement errors for each parameter.

Height

A measure of body size is needed to standardise measures such as weight, and height is a convenient measure to use.

Height was measured on a wall-mounted stadiometer on the ward or in the outpatient department. Shoes were removed and the subject was asked to stand up straight, looking straight ahead with the Frankfurt plane horizontal. The arms were relaxed at the sides, legs were straight and close together, and feet were flat with the heels almost together. The measurement was taken on a hard even floor surface and the subject were instructed to stand as tall as they could. The

instrument was placed on the person's head and, using the spirit level, held in a horizontal plane. The measurement was taken and then repeated; the two measurements had to be within 1cm of each other, if not a third was taken. An average was calculated of the two readings that were within 1cm of each other

Weight

Weight is a convenient and widely used method to assess overall body mass, energy balance and, in conjunction with height, to evaluate nutritional status. A loss of weight over time indicates a negative energy balance and weight gain indicates positive energy balance. As this thesis aims to investigate response to a nutritional intervention it is important to be able to identify a positive energy balance, which would suggest the intervention is successful.

Patients were weighed either in clinic, on a stand on Seca ward scales, which were recently calibrated, using the following methodology:

The scales were positioned near the subject but avoided resting against other furniture. The subject was in nightclothes or light day clothes, heavy items such as jumpers, dressing gowns, jackets and shoes were all removed. Pockets were checked for heavy items and if catheterised, the patients were asked to empty the bladder (or catheter bag emptied). The scales automatically take the reading when movement ceases, and this was then recorded to the nearest 0.1kg.

Percentage weight loss was then calculated using the formula:

$$\% \text{ Weight loss} = \frac{(\text{Usual weight (kg)} - \text{Current weight (kg)})}{\text{Usual weight (kg)}} \times 100$$

The accuracy of the percentage weight loss depends on the accuracy of the original weight estimation before the onset of weight loss. Many patients can give some estimate of their weight when well but the accuracy of the reported weight is questionable [224-226].

Body Mass Index

BMI was calculated from

$$\frac{\text{Weight (kg)}}{\text{Height}^2 \text{ (m)}}$$

Garrow and Webster (1985) [227]

Mid-Arm Circumference

Mid-arm circumference (MAC) is needed to calculate mid-arm muscle circumference (MAMC), which is a practical measure of nutritional status. Alone the MAC can be a guide to overall nutritional state, as it reflects both fat and muscle tissue, or it can be used serially to monitor changes. In this thesis it was used primarily to calculate MAMC, in order to assess muscle mass.

MAC was measured using a flat tape measure (CMS Weighing Ltd), with the subject sitting. If this was not possible, when the subject was bedbound, the recumbent measurement was taken. The non-dominant arm was used wherever possible; to ensure consistency and comparability of the results, because the dominant arm may have a greater muscle volume due to increased use.

First, the subject was asked to bend their arm at a right angle across their abdomen. The length of the upper-arm was then measured from the acromion process of the shoulder blade to the olecranon process of the ulna. The half way point was marked, then the subject was asked to relax their arm and let it hang down by their side, with the palm inwards. The circumference of the arm was measured at the marked mid point, keeping the tape horizontal and taking care not to compress the tissue, but to ensure the tape was not loose with gaps between the tape and the skin. This is often difficult in elderly subjects and patients who have lost significant weight, as they may have a lot of loose skin on their upper arm. In this case the tape was always tightened until the loose skin was gathered in and no gaps existed between the tape and skin. Every effort was still made not to compress the underlying tissue.

If a recumbent measurement was needed, the subject was asked to lie on their back. The mid point was identified as above, and then the arm was laid out

away from the body palm up. The elbow was supported with a rolled up towel to raise the arm from the bed. The circumference could then be measured.

Readings were taken to the nearest 0.1cm and an average of two measurements recorded. Both measurements had to be within 0.5cm, if not further readings were taken, until two measurements within 0.5cm were obtained. The average was calculated from the two measurements within 0.5cm.

Triceps Skinfold Thickness

Triceps skinfold thickness (TSF) is also required to calculate MAMC, but it is also used as a measure of fat tissue. This measurement was chosen primarily to calculate MAMC, but also to provide information on body fat content, possibly allowing the identification of which compartments change during weight changes.

TSF was measured using Holtain Skinfold Calipers (Holtain Ltd., Crosswell, Wales), with the subject sitting. If they were unable to sit up, the measurement was taken while recumbent. The non-dominant arm was used whenever possible, as for the MAC. Firstly, the mid-point was found. In practice the MAC was measured first then the TSF taken using the same mid-point mark. The subject was asked to let their arm hang loosely by their side and a vertical pinch of skin and fat was grasped 1cm above the mid-point mark. This was done at the back of the arm in the mid-line, parallel to the long axis of the upper arm. The pinch was pulled away gently to ensure the muscle layer was avoided, then using the calipers the skinfold was measured at the mid point while maintaining the grasp with the fingers. Care was taken to hold the skinfold gently, so only the calipers were compressing the tissue. The reading was taken to the nearest 0.2mm two to three seconds after applying the calipers.

Three measures were taken, ensuring the pinch was released in between each measure. If the three readings were within 1mm of each other, an average of the three measures was calculated. If not further readings were taken, until three were obtained within 1mm of each other.

If a recumbent measurement was needed, the subject was asked to roll on to their side, so their upper arm was resting along the side of their body. This gave

access to the back of the upper arm enabling the measurement to be taken as above.

Mid-Arm Muscle Circumference

Mid-arm muscle circumference (MAMC) provides a guide to body muscle content. To estimate the arm muscle, MAMC was calculated from Tricep Skinfold Thickness (TSF) and Mid Arm Circumference (MAC) using the following equation [573]:

MAMC (cm) = MAC (cm) – 3.14 x TSF (cm)

Measurement Errors

Investigator error is classed as intra-observer error, which is the difference in repeated measurements by the same observer, and inter-observer error, which is the difference in measurements by two or more observers [574]. Investigators need to be well trained and practiced to produce reproducible measurements.

Functional Measures

It is also useful to study changes in a subject's physical function in addition to observing changes in body size or composition. Functional measures give an indication of changes that will directly influence a person's independence and well-being. Hand-grip dynamometry was used to measure hand and arm muscle strength.

Hand grip strength measures the muscle function of the hand and arm muscles by providing a measure of strength for the gripping action, and it has been shown to correlate well to other measures of muscle function, illustrating that handgrip strength can offer an indication of function and well-being.

There are a number of different types of tool available to measure grip strength including; hydraulic, pneumatic, strain gauge and mechanical [575].

Pneumatic systems such as the Martin Vigorimeter or modified sphygmomanometer are much easier to use for people with hand weakness, pain or deformities, however, they have been criticised for measuring strength as a pressure rather than a force [576]. Pressure depends on the magnitude of the force applied and the area over which it is applied. This means someone with small hands may produce a greater pressure reading than a person of the same strength (equivalent force production) but larger hands.

Strain gauge dynamometers are not usually used in a clinical setting but have been used for research studies. These tools consist of a rigid and a flexible bar, when grasped the flexible bar bends and the transverse force within this bar is measured as it bends. These are very sensitive instruments and can record very small increments of force. They are however, not readily available as most have been individually designed by the investigators [575].

The last type of dynamometer is the mechanical type, which relies on the amount of tension generated on a metal spring, for example the Smedley, Harpenden or Takei Grip-D. The test-retest reliability has been found to be high for this type of dynamometer [575].

The use of grip strength in this thesis is confined to monitoring change, using a Takei Grip-D® dynamometer. This is a mechanical type of dynamometer, consisting of two handles with an adjustable inter-handle distance to accommodate differing hand sizes. The inner handle has to be pulled down towards the outer handle and in doing so pulls on the spring mechanism; the measurement is recorded in kilograms of force (kgf) on a digital display. The measurement range of this equipment is 5-100kgf therefore readings less than 5 are recorded as 0.

The grip strength procedure measures the peak or maximal force produced during a transient grip. The literature is divided over whether the dominant hand is stronger than the non-dominant [575], but when measuring an older population hand disability must be taken into account. Therefore, the subject was asked which their best hand was, and this hand was used rather than the dominant

hand. A note was made which hand was used so serial measurements could be made with the same hand.

When measuring hand grip strength it is important that a standardised position is used for all subjects as the position of the body and arm flexion can influence results [575]. The protocol used ensured that all subjects were seated, their elbow flexed at 90°, with the forearm and wrist in supination (palm face up). They were then asked to grasp the instrument and when ready, squeeze the bars together with their maximal effort. The procedure was repeated three times and the maximum score recorded. A rest of about 15 seconds was allowed between repeated measurements. There is no standard inter-trial rest period in common use, and the time allowed may vary from two seconds to six minutes [575]. The authors [575] have suggested that four minutes are needed to ensure full recovery and eliminate fatigue effects. A shorter time was chosen in these investigations to reduce the duration of the assessment. This may have meant that patients did not always achieve the true maximal grip strength. However, the important factor was the change between two measurements, which would be reliable providing the consistent use of same protocol. Age specific norms for hand grip strength in table 2.2.3 [237, 577].

Table 2.2.3 Reference normal values for hand grip strength

Age range	Female (kgf)	Male (kgf)
* 65-95 years	19.5	33.8
§ 60-69	25.3	45.6
§ 70-79	23.7	42.4
§ ≥80 years	20.0	34.5

** (Bassey & Harries, 1993)[577], using custom built strain gauge dynamometer*

§ (Desrosiers et al, 1995)[578], using Jamar dynamometer

Dietary Intake

Dietary intake was assessed pre-operatively and from the first postoperative day until discharge. Prior to the surgical procedure dietary intake was assessed using 24-hour dietary recall. Post-operatively, fluid and food record charts were the chosen means of recording food and fluid intake. Nursing and support staff were instructed to observe food eaten and to document the amount consumed in household measures i.e. one cup of milk, a half bowl of Cornflakes. Patients were allowed to choose their own food at mealtimes from the ward trolley and were given considerable encouragement to eat. All patients were questioned on their food and fluid intake over the previous 24-hour period to verify the food record charts. Studies conducted in an attempt to quantify the error in dietary assessment methods have found that most estimates using the 24-hour recall are accurate to ±10% of actual food intake [274] [275].

Biochemistry

Pre-operatively and daily post-operatively for the first seven days (as per routine surgical care pathway) serum samples were collected for biochemical analysis of sodium, potassium, urea, creatinine, albumin and C-reactive protein using routine analysis. These samples were sent to the hospital laboratories for routine analysis. If the admitting doctor had already ordered the blood test, it was not repeated.

On the 4-5th post-operative day, a 24-hour urinary collection was performed. Once again this was sent to the hospital laboratories for routine analysis.

The results were usually available within 24 hours on the hospital patient information system. All analysis was carried out using the Abbott Aerosets these instruments are supplied through Abbott Diagnostics USA and the kits used for the following tests are all Abbott CE marked kits.

Nutrition Risk Index (NRI)
The nutrition risk index was calculated using the equation below:

Nutrition Risk Index (NRI)	**Veterans Affairs *et al* (1991) [278]**	NRI= (1.519x albumin, gl $^{-1}$) +(0.417 $\frac{\text{current weight}}{\text{usual weight}}$ X 100 NRI >97.5 borderline malnutrition NRI 83.5-97.5 mildly malnourished NRI <83.5 severely malnourished

Health Related Quality of Life
In addition to indicators of disease, nutritional status and function, measurements of what the patient feels about their own health state have gained increasing interest over the last ten years [579-589]. This is termed 'health related quality of life' (HRQoL).

The World Health Organisation defines HRQoL as:

> *'An individual's perception of his or her position in life in the context of the culture and value systems in which he or she lives and in relation to goals, expectations, standards and concerns. It is affected in complex ways by the person's physical health, psychological state, level of independence, social relationships and how the person relates to salient features of his or her environment.'*
>
> (World Health Organisation, 1998) [445] pg 1569

A primary aim of any treatment intervention is to enhance HRQoL by reducing the impact of disease, but people with severe disease (such as cancer) can still report good HRQoL. Therefore the relationships between health, illness and HRQoL are neither simple nor direct.

An assessment of HRQoL, which is in essence the patients' subjective view of their own health state, adds another dimension to the evaluation of a treatment.

By including this measure the treatment can be assessed more holistically, rather than by focusing solely on defined clinical outcomes.

Types of Health Related Quality of Life Measurements

There are two main types of measure; indices and profiles, and within these categories, tools may be generic or disease specific. The tool chosen for use will depend on the purpose of the evaluation, the population to be studied and the resources available. More complex instruments take longer to complete and some require skilled interviewers. The simpler tools are easier to complete and thus the response rate may be better, but detail is lost as the information collected is limited. For the current RCT the SF-36 was used.

The SF-36

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It has 8 aspects including questions on functional health and well-being scores as well as psychometrically based physical and mental health. It is a generic measure [590] [591].

The SF-36 questionnaire formed part of the initial assessment when subjects were recruited onto the study. The questionnaires were also completed at 6 weeks, 12 weeks, 6 months and 12 months post-discharge. The follow up data was collected by postal survey, and sent to all subjects except those who died. If no response was obtained after one month, a second letter and questionnaire was sent. If no response was received from this letter the follow-up data was treated as missing. Subjects were asked to complete it themselves, or if they preferred they could complete it in the presence of a member of the research team to assist if they had any queries.

A few patients were unable to complete the questionnaire as they simply felt too unwell and did not wish to complete it without help. In this situation, the

instructions and statements that made up the questionnaire were read aloud, and the form completed according to the subject's responses. Care was taken not to prompt replies or make suggestions as to which response was most appropriate. It was important to emphasise that the responses related to how the subject felt on in the last week rather than in general.

The presence of a member of the research team prevented ambiguities, such as patients ticking more than one response in one dimension. There are limitations to this approach, as it is possible that the presence of a member of the research team may influence the subject's responses. Subjects may be influenced in the answers they give due to an awareness of being observed or the supposed wishes of the researcher, known as the Hawthorne effect [592].

The process was also completed on the actual day of discharge or as near to the date of discharge, of the patients from the surgical ward.

Data Analysis of Health Related Quality of Life

The SF-36 questionnaires were manually collated on to the database. The data was then cleaned and checked and subsequently transformed using the 'SF-36 – How to Score Version 2 of the SF-36 Health Survey [593].

Cost Analysis

It is assumed that patients who have a prolonged LOHS have increased healthcare expenditure [594]. A key priority of healthcare organisations is to reduce healthcare expenditure whilst maintaining and improving quality clinical care.

A report from the USA, suggested that surgical services represent approximately 40% of all hospital expenditure, thus, any interventions that can potentially reduced expenditure are important [595].

Therapies that lower morbidity and mortality have traditionally been perceived as effective by clinicians, regardless of cost. The two terms 'effective' and 'clinically effective' should be interchangeable however this is not always the case.

Recently, pragmatic clinical trials have included a financial analysis in the outcomes to determine if treatments are justified [12, 596]. Often, data on cost can be collected concurrently with other outcome data in a pragmatic RCT [597].

Cost effectiveness analysis compares the cost of the treatments with their relative effectiveness. If the costs of the intervention are less than the control, and its effectiveness is superior, then the intervention is 'dominant' and should be accepted. If the cost of the intervention is more than that of the control, and its effectiveness is inferior, then the control treatment is dominant and the intervention should be rejected.

If however, the intervention treatment is cheaper than the control or less effective, or vice versa, then there is a trade off and an assessment of the relative size of the difference in costs, compared to the difference in effectiveness is needed. An alternative approach is to measure the subjects' health utility, in order to calculate 'Quality Adjusted Life Years' (QALYs).

There are several factors that need to be considered in a cost analysis, these include,

1. Cost benefit analysis attempts to put a monetary value on the health benefits of a treatment. However, assigning monetary value to health outcomes is not always seen as appropriate by clinicians.

2. Costing is rarely straightforward as there are many factors that need to be taken into account when making cost comparisons. Assumptions need to be made that would probably be unacceptable across other scientific disciplines.

3. Capital costs include building, equipment costs and land and other capital-intensive items (expenditure on structural alterations).

4. Overhead costs are those resources related to the building (power supply, water rates etc) staffing costs and other costs of providing the service (catering, laundry, maintenance, cleaning, stationary).

5. Resource costs are those costs related to the treatment of the patients (use of investigations, biochemistry costs, and procedures, costs of drugs prescriptions and interventions.)

For the purpose of this RCT, a full health economic study was deemed inappropriate, as this would have required additional economic and staff resources to support the collection of the data and analysis. This was considered to be outside the remit of this RCT. Cost of capital, overhead and resource costs are considered to be the same for both groups of the study.

An alternative approach is to present arrays of outcomes alongside their costs and leave the reader to draw their own conclusions regarding the cost. This is termed the cost consequence analysis. This is the approach used in this RCT.

A cost calculation was performed based on the median and interquartile range of length of hospital stay and development of the statistically significant complications, for the two randomised groups. This has been used as an end point in other clinical trials as a crude indicator of cost [12, 13] but never the less is a general indication of cost comparison. In addition, the costs of treating the statistically different major complications for the two groups were also calculated.

2.1.7 Reliability and Validity of the Study

Reliability and consistency of the study itself is also an important consideration in terms of clarity and accuracy of the final report. In qualitative terms reliability is referred to as consistency, repeatability, replicability or stability of the study [598-600].

In order to ensure good quality of the study a number of factors have been used to ensure rigor.

Care was taken throughout the study to ensure that no other intrinsic or extrinsic factors could influence the results within either of the groups. This was addressed with:

1. Stringent inclusion and exclusion that prevented changes in clinical interventions without discussion with the investigator.

2. The use of random allocation enabled all the subjects to have equal opportunity to be included in either the standard or treatment groups.

3. The use of reliable and valid assessment measures as outlined in the clinical outcome section.

4. Consistency of approach across all four hospitals sites, by only the Research assistant and PI collecting data and implementing the protocol.

5. A robust training and educational programme was set up prior to commencing the RCT.

6. Engaging the support of all relevant stakeholders to ensure the RCT protocol was adhered to.

7. Stringent data management programme as outlined in section 2.3.

2.1.8 Summary

This section has outlined the trial design. It has discussed the aims and objectives of the current RCT that is presented in this thesis.

This was then followed by a detailed justification for the choice of Outcomes (both Primary and Secondary Outcomes) along with a clear definition that would be the basis for data collection and analysis.

In addition, an overview of the important issues that are required to be considered to ensure the reliability and validity of the study.

The next section will outline the study procedures for the trial progress of the current RCT.

2.2 Study Procedures for the Randomised Controlled Trial

2.2.0 Introduction

This section will present the study procedures for the RCT presented in this thesis. It will outline the principles of the trial design and trial progress. It will also detail methods for data management and data analysis.

2.2.1 Sample Population

The patients were recruited as a convenience sample. Thus, all patients who underwent major resection for upper gastrointestinal cancer under the remit of the South East Wales Regional Upper GI cancer Network were eligible to be recruited into the study.

2.2.1.1 Inclusion Criteria

All patients admitted to the adult Upper Gastrointestinal and Hepatobiliary Unit at the 4 hospital sites with a suspected upper gastrointestinal malignancy and referred for major elective or semi elective operative resection, were eligible to enter into the trial on the approval of their Consultant Surgeon (no patients were refused entry by their Consultant).

2.2.1.2 Exclusion Criteria

Patients were excluded if any of the following existed:

1. They were unable or unwilling to give informed written consent

2. They had a pre-operative infection

3. They had a residual small intestine length of less than 100cms resulting from previous intestinal surgery

5. They were under 18 years of age.

6. They were pregnant

2.2.1.3 Sample Size Power Calculation

Following discussion with two independent Statisticians, it was anticipated that 80 patients in both groups of the trial would have an 80% power to predict a 3 day reduction in length of hospital stay (total N = 160). This was based on the results of the pilot study (appendix II.I). The desired significance level was set at 0.05%, therefore, the risk of a Type I error is 5%.

The power was set at 0.80, thus the study should have an 80% chance of detecting a treatment effect and the risk of Type II error is 20%.

2.2.2 Registration and initiation of the Clinical Trial

2.2.2.1 Ethical Approval

In order to proceed with the study ethical approval was obtained. Approval was obtained from the Local Ethics Research Committee, as all the hospital centres were located in the same 'domain'. The approval was based on a "no local researcher" basis that meant that the PI had to perform all consenting and recruiting of patients in the RCT. The letter of permission from ethics committee is in appendix II.II.

As nutritional products are classed as borderline substances advice was sought from the Medicines for Human Use Regulations (MHRA) 2004 who regulate trials on medicines for humans. Following discussion and scrutiny of the research protocol by the MHRA, the consensus was that the use of nutritional support are not classified as drugs and the trial did not meet the criteria of the EU Clinical Trial Directive.

However, in line with 'best practice' the trial was conducted in line with the Research Governance framework and MRC guidelines for conducting clinical trials [601]

In accordance with the Research Governance Framework [557], local Hospital Trust Research and Development approval was obtained at each of the 4 hospital centres. The trial was subsequently registered on the National Research Register (NRR) [602].

The trial protocol was scutinised by the the Welsh Cancer Trial Network and the UK National Cancer Trials Network (NCTN) [603] and adopted and registered on the NCTN database of Cancer clinical trials.

In addition, the study protocol was peer-reviewed by experts in the field of surgical nutritional support during the grant application. External grant funding was obtained from the Health Foundation, London, UK [604] and also funding was secured by the Cardiff and Vale NHS Trust small grant award scheme. This enabled a pilot study to be conducted N=8 (appendix II.I). Amendments to the research protocol were made following the pilot study; these are detailed in appendix II.III.

2.2.2.2 Sponsorship of Study

The Research Governance Framework requires that all clinical trials have a 'Sponsor'. For this MCRCT the employing organisation of the Principal Investigator, Centre 1 provided sponsorship for the trial. The Sponsor acts to take responsibility for securing the arrangements to initiate, manage and finance clinical trials.

All relevant Stakeholders of the trial were kept fully informed of the progress of the clinical trial in order to ensure appropriate adherence to the protocol.

2.2.3 Recruitment of Patients into the Trial

The PI approached eligible patients at least 48 hours after the diagnosis of a UGI malignancy or a suspected malignancy, which required surgical resection. A detailed verbal explanation of the trial was provided. The PI explained the purpose of the trial, and that all data provided would by kept anonymous and confidential. This was outlined in the patient information sheet (appendix II.IV).

Patients were allowed a minimum time of 12-24 hours from being given the patient information sheet and signing the consent form.

After agreeing to participate in the trial the patient was asked to sign two copies of the consent form (appendix II.V), one was put in the medical notes and one was kept in a locked filing cabinet, along with the data collection proforma.

The PI also assured the patient that at any time they could withdraw from the trial and that all data collected would be kept in accordance with the Data Protection Act (1998) [605].

Patients were reassured that they could contact either the PI or the on-call surgical registrar to discuss further any aspect of the trial. The PI was aware of the sensitive nature of this trial and that these patients may require more time to give informed consent, after receiving their diagnosis of cancer.

2.2.3.1 Randomisation and Stratification

For the purpose of this RCT, stratification was based on each hospital centre, thus there were four separate randomisation sequences. The unit of randomisation was the patient. This study used an unrestricted method of random allocation. The randomisation was performed in blocks of 30 to ensure all patients are exposed to similar care and that alterations in care and staff have not changed.

Fifteen pieces of paper with EEN written on and 15 pieces of paper with STD written on were placed in sealed opaque envelopes. These envelopes were then shuffled and then labeled 1-30. All envelopes were kept in a locked box in the main research site. Each envelope contained instructions as to whether the patient would receive standard management or receive early enteral nutritional support.

The randomisation envelopes were opened at the end of the operation after the PI was confident that a potentially curative procedure had been performed. The investigator conducted the randomisation in order to ensure that chance and not choice, determined the allocation procedure.

2.2.3.2 Blinding

Following discussion with the research team and the multidisciplinary team it was considered impossible to blind the groups in this RCT. Blinding was neither practical nor feasible in this clinical trial. This is discussed in the limitations of the RCT in the discussion chapter 4.0.

The patients were kept ignorant to which allocated group they had been randomised to for the first week after surgery, unless they asked specifically. This was made easier as the patients were often on the critical care unit and were typically unaware of the presence of the enteral feed.

2.2.3.3 Patients who declined Consent

All patients eligible for entry into the study had preliminary baseline data collected. This is important to determine if the reasons indicate that those who do not wish to participate constitute a separate sub group. This group was subjected to statistical analysis, in comparison with the responders to ensure they did not differ from the main study population.

2.2.4 Non-Interventional phase

2.2.4.1 Pre-operative Stage

Following the patient being recruited to the trial, the following data were collected prior to surgery:

1) Oral dietary intake in kilocalories/day and oral dietary protein intake/day.

2) Current weight, self reported pre-illness weight, percentage weight loss

3) Body Mass Index (BMI)

4) Appetite changes, taste changes, swallowing and chewing ability

5) Tricep skinfold thickness, mid upper arm circumference, muscle strength (using hand-dynanometry)

6) Routine clinical biochemistry: liver, renal and bone profile, albumin and C-reactive protein

7) Sex and age of the patient

8) The SF-36 Health Related Quality of life questionnaire [606]

9) Medical and surgical history from doctor's clerking

10) The diagnosis/stage of the primary malignancy and whether neo-adjuvant chemotherapy had been administered.

2.2.4.2 Intra-operative stage

Patients were randomised at the conclusion of the laparotomy. All patients had a needle catheter feeding jejunostomy inserted by the operating surgeon. (A jejunostomy was inserted to ensure that if patients did develop complications preventing them from achieving adequate oral intake, enteral feeding could be commenced after 5-7 days.) The jejunostomy was inserted at 30-100cms distal to the Duodenal-Jejunal flexure. The type of jejunostomy was a Freka®Fresenius *Fg* 9 needle catheter jejunostomy.

The following data were recorded whilst the patient was in the operating theatre: The case report forms (CRFs) are presented in appendix II.VI.

1) Type of anaesthetic used and method of post-operative analgesia

2) Estimation of intra-operative fluid Balance (in millilitres).

3) Intra-operative blood loss (in millilitres)

4) Duration of operative procedure (in hours). This was recorded as the time from induction of anaesthetic to the patient leaving the operating theatre.

5) The type of surgical procedure performed. These are classified as Oesophagectomy, Gastrectomy or Pancreatectomy.

Any patient who underwent a palliative resection was recorded and subsequently excluded from the RCT.

2.2.5 Interventional Phase

This section will outline a comparison of the intervention groups forming the basis of the RCT. There were two groups for comparison.

2.2.5.1 Choice of Interventions

For the purpose of this study the experimental intervention was early enteral nutrition compared with standard therapy.

Group A (Standard Therapy Group)

The patients in this group received standard treatment. The standard group received 10ml/hour of sterile water via the needle catheter jejunostomy. Hydration was maintained using intravenous fluids. This continued until the introduction of oral fluids and diet.

All patients in the trial continued to receive the appropriate clinical treatment as decided by their surgical and critical care teams. All patients had a radiological

contrast swallow between days 7-10 days after the operation. It was following this 'swallow' test that patients were deemed 'safe' to swallow and then oral fluids and diet were gradually introduced over 2-5 days at the patients' preference.

If the 'swallow' tests deemed the patient unsafe for initiating oral diet and fluids this was recorded. If oral intake had not resumed by day 8, patients in the standard group were reviewed as to the need for either enteral or parenteral nutritional support. This was administered at the discretion of the operating surgeon. Nutritional requirements were calculated based on 30 kcals per kg per day [572]. To mimic the introduction of oral diet the feed rate was gradually increased over 2-5 days.

Group B (Enteral Nutrition Group)

In addition to standard management, these patients commenced early enteral nutrition via a needle catheter jejunostomy (Freka® *fg* 9 Fresenius). Nutritional support was commenced within 12 hours of leaving the operating theatre. However, patients were not started on enteral nutritional support if they were clinically and haemodynamically unstable.

Feeding Protocol

The enteral nutrition group was started on enteral feed administered at 10 ml/hour for the first 24 hours, via the needle catheter jejunostomy. On the first post-operative day enteral feed was increased to 20ml/hour for 12 hours and 30 ml/hour for next 24 hours. The feed was then increased by 10mls/hour until the maximum target rate of feed of 80ml/hour was achieved. Nutritional requirements were calculated [572]. The enteral nutrition formulas were polymeric 1 kcal/ml commercial preparation for gastrectomy and oesophagectomy patients and 1.3-kcals/ml semi-elemental formula for the pancreactectomy patients.

It was intended to achieve a minimum of half of nutritional requirements by day 5 post-operatively.

Once oral intake had commenced, the patient was commenced on a 1.5 kcal/ml enteral feed. The patients were switched to receive overnight enteral nutrition (12 hours) until it was deemed that the patient was achieving ¾ of their nutritional requirements orally.

2.2.6 Post Operative Stage Data Collection

All patients were prospectively followed up and the following data was collected daily: (appendix II.VI).

1) Ward location

2) Type of feed administered

3) Rate of feed in millilitres

4) Percentage of nutritional requirements delivered via the jejunostomy per 24 hours (Nutritional requirements were calculated using Elwyn (1980) [572]

5) Presence of nausea and vomiting.

6) Presence of abdominal distension.

7) Fluid balance in millilitres per 24 hours.

8) Passage of bowel motions (i.e. flatus, diarrhoea and constipation).

9) Frequency of peristaltic waves per minute as detected using ultrasound imaging

10) Presence of both major and minor complications (see appendix iv)

11) Routine post-operative biochemistry liver: renal and bone profile, albumin and C-reactive protein

12) Routine post-operative full blood count

13) Temperature from the nursing records. The highest daily temperature per day was recorded

14) Pain score and Analgesia requirements was recorded using the nursing records

15) Stage of mobilisation

2.2.6.1 Discharge

On the day of discharge the following information was collected. All patients were discharged with their needle catheter jejunostomy *in situ* until their first outpatient clinic appointment at 2-6 weeks. On discharge the following data was collected (appendix II.VI):

1. Weight and percentage weight loss post-operatively
2. Mid Upper Arm Circumference, Tricep Skinfold Thickness and muscle function
3. Serum albumin
4. The presence of any minor or major complications
5. The need for home enteral nutrition
6. SF-36 Health Related Quality of life questionnaire [606]
7. The destination to where the patient was discharged.

2.2.6.2 Follow-up

Patients were reviewed at 6 weeks and 12 weeks post discharge at their routine outpatient appointment. The following information was collected (appendix II.VI):

1. Weight and percentage weight loss post-operatively
2. MUAC, TSF and muscle function
3. The presence of any minor or major complications
4. SF-36 Health Related Quality of life questionnaire [606]
5. Readmission to hospital rates and the duration of stay if applicable

2.2.6.3 Close of Study

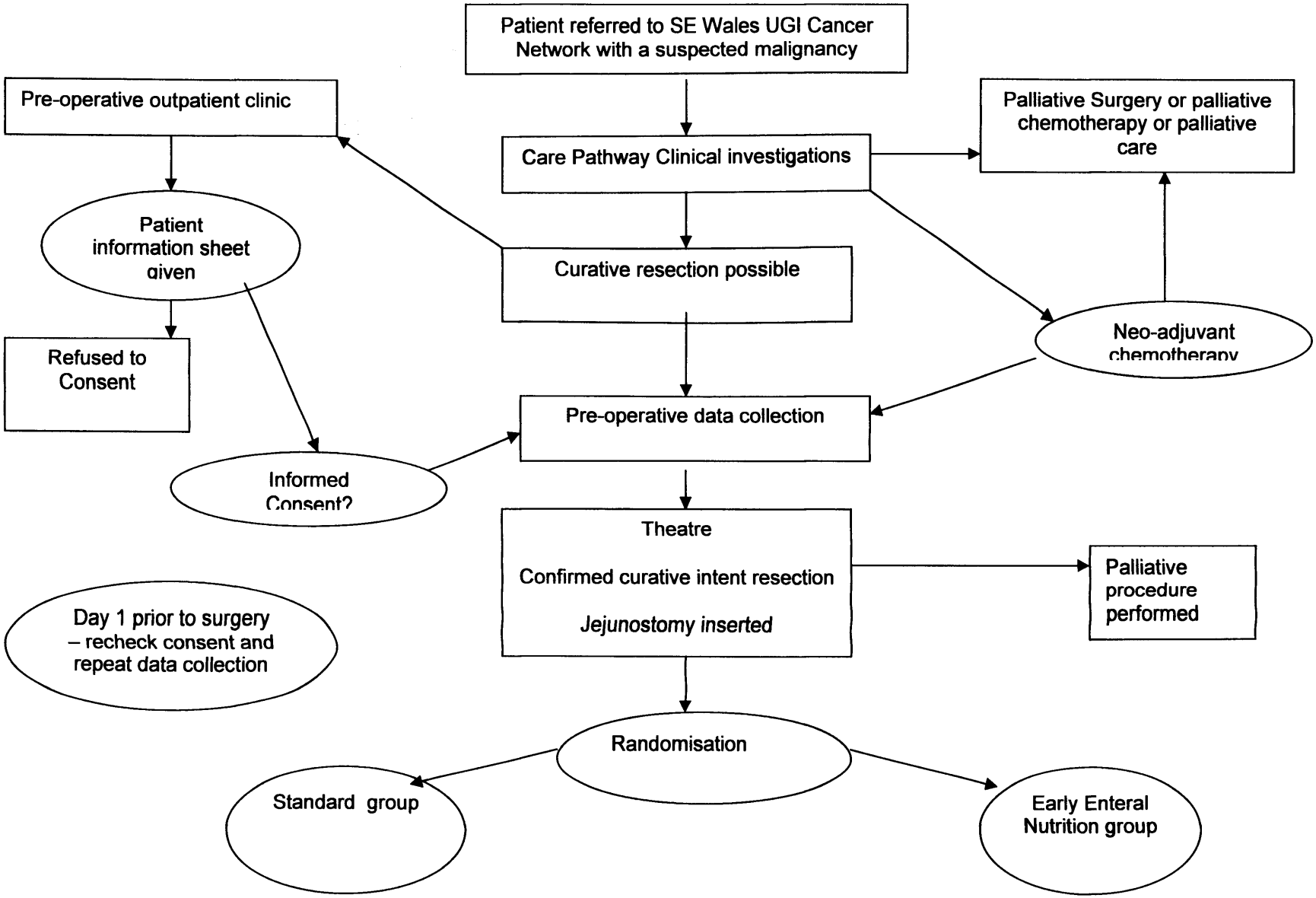
The patients were contacted when they attended outpatient clinic as near to one year as possible to prevent the patients having to be contacted independently of this appointment. The following information was collated at one year.

1. SF-36 Health related Quality of life questionnaire [606]

2. Survival rates

For the purpose of this thesis however, this data will not be included as it was still being collected when a cut off was made.

2.2.7 Summary of Methods



2.3 Data Management

2.3.0 Introduction

The next section will detail the factors that were considered regarding the data management of the current Randomised Controlled Trial. It will outline the issues for quality control, data validity and cleaning and data analysis.

2.3.1 Quality Control

The data were entered by hand onto the case report forms (CRFs). The CRFs were developed in collaboration with the Trial Steering Committee. The database was developed in the statistical software package SPSS 12.0 (*SPSS Inc.*, Chicago, USA)

The PI checked quality and consistency of data entry for every third patient. Following the securing of funding for a research assistant, the Research Assistant (RA) helped the PI with the data collection. A rigorous training programme was provided for the Research Assistant. This included spending time with other RAs in the Welsh clinical Trials units and attending several courses on data management and SPSS.

The PI verified at regular intervals that data collection was accurate and that CRFs had been completed correctly. Regular 'spot' checks of the data base and data collection sheets were conducted to ensure consistency and accuracy.

2.3.1.1 Data Validity and Cleaning

The first stage in the 'cleaning' process was to tidy up the database. All the variable names were checked to ensure they were easily understood and corresponded correctly with the data, and categorical variables had each category labeled correctly. In addition, each variable was checked to ensure it registered missing data correctly.

Once these checks were made, the subject numbers were examined to ensure they were all present and that all the numbers were the same for each section of data. Once completed many of the duplicate variables could be deleted to make the database more manageable.

The next part of the process was the systematic cleaning of all the data. For many of the variables logical checks could be made for errors. Some variables should have no missing data, such as age, sex, ward, LOHS or randomisation group. Any missing data that could be obtained from the hospital patient database was added to the database. As length of hospital stay was the primary outcome indicator this was doubled check prior to the final data analysis. Once these logical checks had been made, additional variables were added. For example, to identify the patients who died and which arm of the study patients were in. Next, each continuous variable's range was analysed and any results outside reasonable values were double-checked with the written CRF. For example, weight above 110kg and below 30kg, values outside this range could still be valid but were unlikely, so were verified as far as possible. No values were deleted at this stage but merely cross-checked. Some variables had set limits, in this case the original CRF was checked and if the correct figure was not apparent, the figure in the database was deleted and treated as missing.

Categorical data were checked to ensure only the appropriate categories were present, for example, appetite was scored from 1-5 therefore any number other than these was erroneous.

As the variables had all now been examined in detail for errors, derived variables could be calculated, such as the mean of multiple anthropometric measures, BMI, MAMC, and the changes between variables from the first and second assessments. In addition, time spans were calculated from dates to produce the variables such as length of stay and survival.

Once these were calculated the outliers were studied, in SPSS these are produced as the five most extreme values at either end of the distribution. Any 'impossible' values were removed at this stage; the definition of 'impossible' was agreed through careful discussion with supervisors and others interested in the research project (see acknowledgements). In the event very little data needed to be removed, and these were mainly from the variables calculated to show the changes during the study. As an example, weight change for a subject who had gained 22.3 kg, which was impossible within the length of time they were on the

study. The original data were checked to try to establish the correct values and if this was not possible all related values were deleted i.e. the weights from assessment one and two and the change value, as it was impossible to tell which of the two values was incorrect. During this screening process the data distribution was also observed to look for parametric and non-parametric distributions. A copy of the final database was burnt onto a CD and kept in a locked cabinet.

2.3.2 Data Analysis

The types of statistical methods are dependent on the design of the study and the type of data collected. Data analysis include descriptive statistics that describe the sample characteristics and inferential statistics that assist in making an inference regarding the population based upon the evidence from the study.

2.3.2.1 Intention to Treat Analysis

'Intention to treat' is a strategy for analysing the results of RCTs according to the original treatment allocation. This includes participants that did not receive the allocated treatment. There could be many reasons why patients may not have had received their allocated treatment: These included:

1. Non-compliance with treatment
2. Dropped out from follow up
3. Underwent co-interventions
4. Dissatisfaction with treatment allocation

All these reasons should be detailed on the CONSORT flow diagram, so all allocated patients can be accounted for.

The intention-to-treat approach is assumed to represent a 'real life' situation with respect to compliance and treatment errors [607] and it is thought to give a more realistic assessment of the treatment in usual clinical practice [550]. Failure to conduct 'intention-to-treat' analysis has been reported to overestimate the treatment effect [608]. The current RCT aimed to analyse the primary outcome on an 'intention-to-treat' basis and a Per Protocol Analysis.

2.3.2.2 Per Protocol Analysis

This is often an alternative to 'intention-to-treat' analysis. Subjects are included for analysis only if they complete the treatment as *per protocol*, however Altman (1990)[541] criticised this analysis as leading to bias.

2.3.2.3 Interim Analysis

This is an analysis that is carried out before the trial has finished, usually to check safety, problems with recruitment and unexpected side effects for one of the arms. For the purpose of the current study an interim analysis was conducted at 12 months after the trial commenced.

As mentioned previously, this thesis reports the results of a pragmaic early analysis of the first 102 patients in the current RCT. This was due to the time constraints of the need to complete the thesis within the deadline of the University for submission.

2.3.2.4 Withdrawals and Drop Outs

Poor compliance with treatment and loss to follow up lead to the exclusion of patients after they have been randomised to their treatment groups. Dropouts and withdrawals were reported on the CONSORT flowchart [559] [558]. The reasons for reporting the exclusions in a robust manner centres on a paradox called the 'Exclusion Paradox' [609]. This states that if trialists do not report exclusions, the reader assumes the trial did not have any. Therefore this may bias the interpretation of the results of the study.

Missing data are inevitable in any clinical trial and there are several methods for dealing with it [610]. Firstly missing data can be ignored, secondly the last observed value can be carried forward, finally a regression method or imputation can be used. For this trial, the last observed value was used.

2.3.2.5 Stages of Data Analysis

RCTs typically measure continuous, categorical and ordinal variables at baseline, which are then repeated at intervals after the introduction of the treatment intervention in two or more groups. Analysing the results can be divided into:

1.Baseline comparison of the two groups (descriptive statistics)

2. Primary analyses- intention to treat analyses of primary outcome

2.3.2.6 Baseline Comparison

Despite the randomisation process, which aims to produce groups, which are equal, there may be some baseline differences between the two groups occurring by chance. If this occurs then more complex statistical methods such as ANCOVA can be used. However these methods have been widely criticised [611]. Senn (1997) [611], stated that using these statistical methods at baseline complicate baseline comparability.

For the purpose of the current RCT, patient variables analysed included; age, gender, and other peri-operative treatment variables (type of operation, operative blood loss, operative duration, POSSUM score, use of neo-adjuvant chemotherapy) associated with influencing the primary outcome indicator [565, 566] as outlined in section 2.1.6.1.

The randomised groups were compared at baseline (pre-operatively) to determine if the groups were similar for these confounding factors. The statistical analyses used for this were based on descriptive statistics such as means and medians, depending whether the variable was normally distributed. Pre-operative nutritional parameters were also compared at baseline for the two randomised groups. Once again descriptive statistics were used for these comparisons.

2.3.2.7 Primary and Secondary Analyses of Outcomes

The primary outcome indicator (LOHS) was analysed on an intention-to-treat and per-protocol basis. Length of hospital stay was not normally distributed so it is presented as median with the range of inter-quartile points. Where data were normally distributed, mean and standard deviation (SD) were presented.

Univariate analysis was performed using the Mann-Whitney *U* test for continuous data that was not normally distributed. The Chi-squared test was used for categorical data and the Fischer's exact test was used if the data sample was small, thus the assumptions for the chi-squared test could not be met. If the data were normally distributed a parametric test could be used, namely the two sample t-test. $P< 0.05$ was accepted as significant. All P- values reported were two tailed.

2.3.3 Summary

This section has detailed the procedures for conducting the RCT described in this thesis. It has discussed the sample population, the eligibility criteria and has reported the power calculation on which the funding and execution of the trial was initially based. It has presented the administrative procedures required to ensure the trial was ethical and registered according to the recommendations required in the Research Governance Framework.

It then presented how the recruitment and subsequent accrual was to be performed. This was followed by details of the randomisation and stratification procedures. It also presented the trial progress detailing both the interventional and data collection phases. The section then ended with the methods used for data management including, data cleaning, data checking, quality control and data analysis. The next chapter will present the results of the RCT.

3. Results

3.0 Introduction

The purpose of this chapter is to present the results of an early analysis of the Multicentred Randomised Controlled Trial (MCRCT) of early enteral nutrition versus standard management for patients undergoing major resection for upper gastrointestinal cancer.

The chapter is subdivided into:

1. Trial Profile
2. Baseline Characteristics
3. Primary analysis of Results
4. Secondary analysis of Results

3.1 Trial Profile

Initially, the RCT was a Single Centre study, but evolved to become Multicentre during the RCT. Three additional hospital centres were enrolled to recruit patients. This was to:

1. Improve the accrual of patients
2. Enable the recruitment of all patients who had their surgical treatment performed by a surgical member of the Local Regional Upper Gastrointestinal Cancer Network.

All patients eligible for entry into the MCRCT had their optimum treatment option (i.e. surgical, oncological or palliative care) discussed at a weekly Multidisciplinary Team (MDT) meeting. Therefore the decision to perform elective curative intent resection was based on a consensus agreement within the MDT.

3.1.1 Descriptions of Referring Hospital Centres

Centre 1: A University Teaching Hospital.

This centre was the base of the principal investigator and author of this thesis. The hospital is the main centre, serving a population of 1.3 million (WAG (2006)).

Surgical procedures performed at this site include oesophagectomy, gastrectomy, pancreatic and biliary resections. Recruitment was completed from November 2002 to July 2006. There were 3 operating consultant surgeons at this centre, referring patients to the MCRCT.

Centre 2: A District General Hospital

Centre 2 was located 12 miles from Cardiff. It serves a population of 560,000 people (WAG (2006)). There was one upper gastrointestinal surgeon performing both oesophagectomy and gastrectomy. This site recruited for 8 months from October 2004 to May 2005. The operating surgeon then relocated to Centre 1, becoming the 3rd surgeon there. This centre subsequently stopped recruiting patients to the MCRCT.

Centre 3: A District General Hospital

Centre 3 was located 18 miles from Cardiff. This centre also had one referring upper gastrointestinal surgeon performing oesophagectomy and gastrectomy. This centre referred patients to the study for 20 months from December 2004 to July 2006.

Centre 4: A District General Hospital

Centre 4 had one operating surgeon performing both upper gastrointestinal and pancreatic resections. This centre did not recruit any patients successfully into the trial. During 3 months (January 2006 to April 2006) all patients eligible were deemed palliative at laparotomy.

3.1.2 Referrals of Patients into the Trial from each Hospital Centre

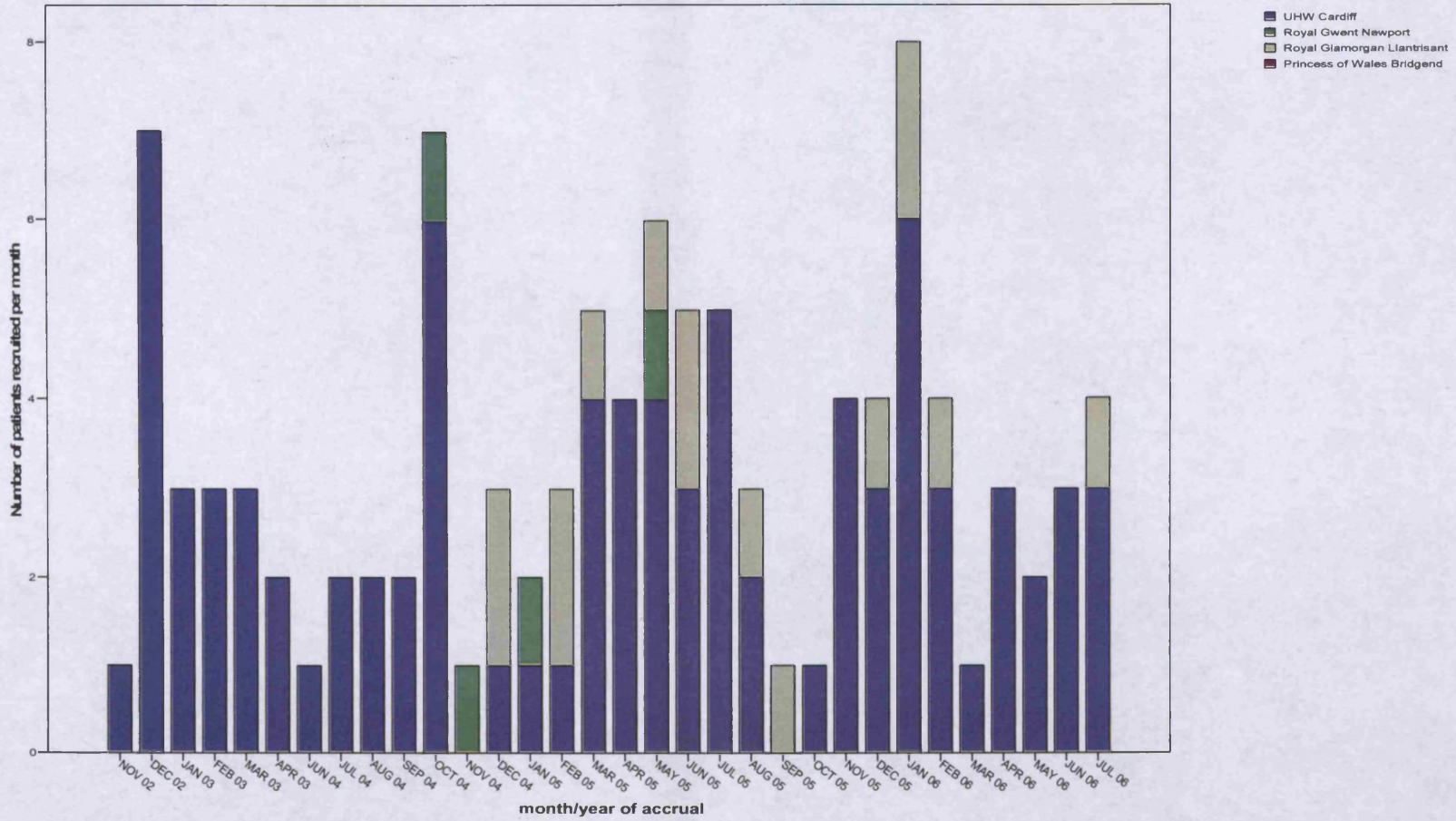
The RCT recruited patients from November 2002 to July 2006. Recruitment by hospital centre is illustrated in table 3.1.

Table 3.1 Recruitment of patients in each of the Randomisation groups per hospital Centre.

Hospital Centre	No. of Months trial active	No. of Patients approached	No. of patients recruited
Centre 1	30	108	85
Centre 2	7	3	3
Centre 3	18	21	14
Centre 4	3	4	0

The number of patients recruited varied over the course of the MCRCT. The monthly recruitment rates are presented in figure 3.1. The months with a peak number of patients recruited was December 2003, October 2004, May 2005 and January 2006, each month recruiting 6-8 patients.

Figure 3.1 Monthly Recruitment of patients in each of the Randomisation groups per hospital Centre.



3.2 Trial Progress

The number of patients eligible for entry into the MCRCT at the point of cut off for this thesis was 169 patients. A total of 139 patients were recruited into the trial. The consent rate was 82.2%. Only patients who underwent curative intent surgery were eligible to be randomised. Therefore, it was inevitable that a proportion of the patients recruited would not be randomised following laparotomy and palliative surgery only. Thirty-seven patients were deemed palliative at open operation. Therefore, 102 patients were randomised for entry into the MCRCT.

Sixty patients were randomised to receive early enteral nutrition and 42 patients were randomised to receive standard management. There was an imbalance of 18 patients between the two groups when the MCRCT closed for the analysis for this thesis. Whilst surprising, this can be explained by the block randomisation. Centre 1 did not complete the full third block of 30; and the other two centres recruited less than 30 patients. (The randomisation was performed in blocks of thirty by each centre as described in the methods chapter.)

The trial progress is summarised in the CONSORT diagram (figure 3.2).

3.2.1 Sample Characteristics

All patients in the MCRCT were admitted for major upper gastrointestinal or hepatobilary surgery. The most frequently occurring diagnosis was oesophageal cancer, 47% (N=48). Twenty-nine patients (28%) presented with gastric carcinoma and 25 patients (24.5%) presented with pancreatic cancers. The median age of the population was 64 years (58-72 years).

The surgical procedures performed at each hospital centre were compared. Centre 1 carried out the majority of all surgical procedures (N=86). The number of surgical procedures in Centre 2 and 3 were too small for meaningful comparisons. Only centre 1 conducted pancreatic resection. The types of surgery are presented in table 3.2.

Table 3.2 Comparison of the Surgical Procedures Performed at each Hospital Centre

	Hospital Centre		
	Centre 1 N (%)	**Centre 2 N (%)**	**Centre 3 N (%)**
Transhiatal oesophagectomy	15 (83%)	0 (0)	3 (17)
Ivor-Lewis oesophagectomy	20 (69)	2 (7)	7 (24)
Partial Gastrectomy	15 (100)	0 (0)	0 (0)
Total Gastrectomy	11 (79)	1 (7)	2 (14)
3 stage oesophagectomy	0 (0)	0 (0)	1 (100)
Total Pancreactectomy	2 (100)	0 (0)	0 (0)
PPPD	23 (100)	0 (0)	0 (0)
Total	86 (84)	3 (3)	13 (13)

3.2.2 Description of Patients who declined consent

Thirty patients declined consent for the MCRCT. Fundamental demographic and oncological data were collected on these patients to enable a comparison to be made with the randomised study population. The results are presented in table 3.3.

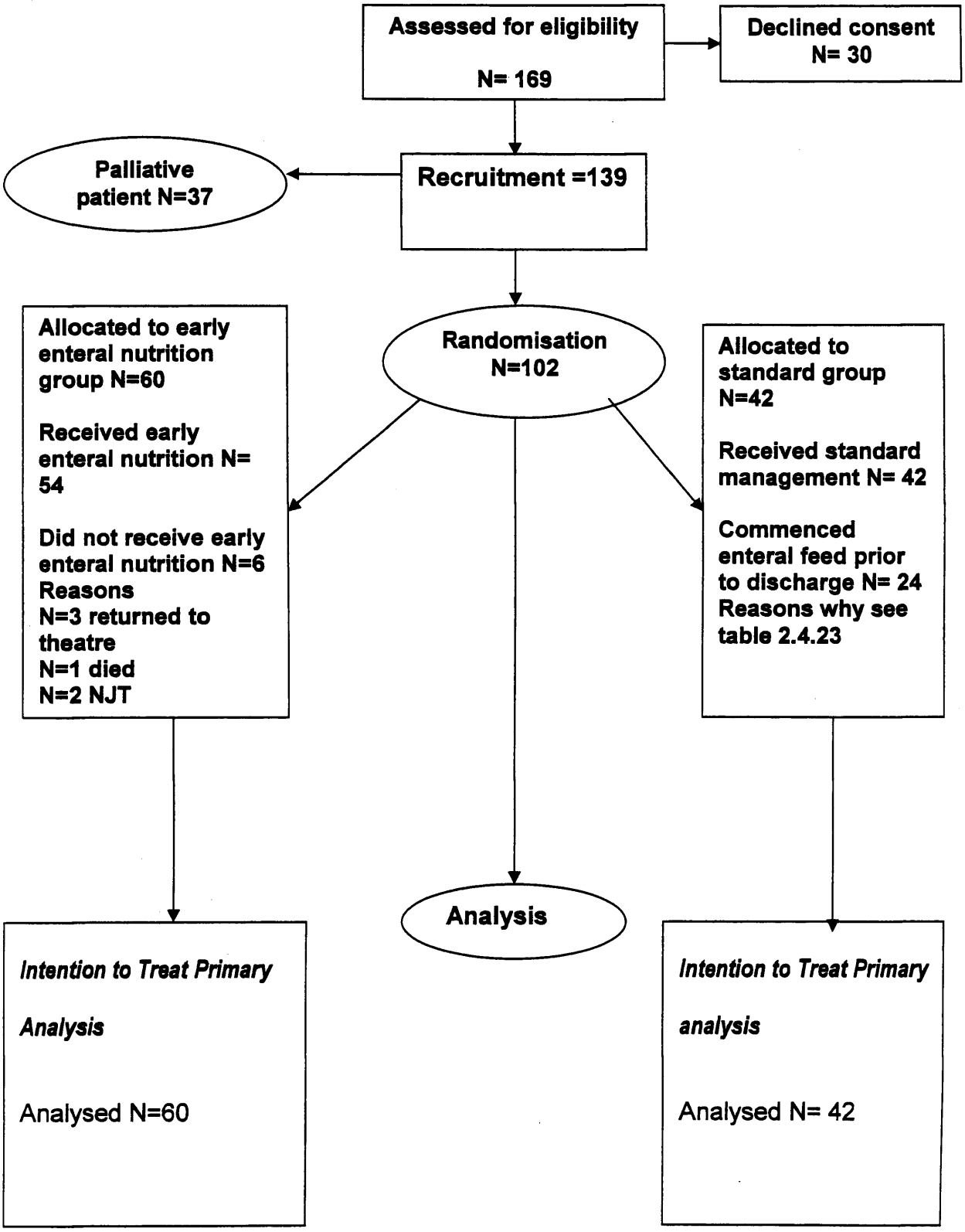
Table 3.3 Baseline variables for patients who declined consent and patients who were randomised into the RCT

	Declined Consent N=30	Randomised Group N=102	Chi (p)
Age median	62 (53-76)	64 (58-72)	NS
Gender N (%)			NS
Male	16 (51.6)	64 (68)	
Female	15 (48.4)	33 (32)	
Type of Tumour N (%)			NS
Oesophageal	10 (32.25)	46 (47)	
Gastric	11 (35.5)	28 (28)	
Pancreatic	10 (32.25	23 (23.7)	
Staging N (%)			
I	9 (29)	11 (11.5)	7.59 (0.033)
II	15 (48.4)	43 (44.5)	
III	7 (22.6)	39 (40.5)	
IV	0 (0)	3 (3.5)	
Histology			
Adenocarcinoma	25 (80.6)		
Squamous Cell	6 (19.4)	NA	

There were no statistical differences for age, gender and type of tumour between the randomised patients and the patients who declined consent.

There was a statistical difference (Chi 7.59 p=0.033) for pre-operative staging of tumour. Thirty (40.5%) of the patients recruited and randomised presented with tumour stage III or above. This is compared to 22.6% of the patients who declined consent. This suggests that the patients in the RCT had more advanced tumours than the patients who declined to consent.

Figure 3.2 CONSORT Diagram



3.3 Baseline Sample Characteristics

The two randomised groups were compared at baseline. This section presents baseline comparisons of the demographic data, peri-operative factors, nutritional parameters and biochemical parameters.

This section did not undertake hypothesis driven analysis. If certain characteristics looked potentially different, then exploratory inferential analysis was performed. This was to limit the chance of a Type I error.

3.3.1 Baseline Comparison of Age and Gender

There were no differences between the two-randomisation groups for age and gender, in both groups the majority of participants were male (1:2 male: female) and the youngest participants were in their fifties. This data is shown in table 3.4.

Table 3.4 Age and Gender of the Randomisation Groups.

Variable	STD group	EEN group	Total population
Age median (IQ range)	63.5 (56-73)	63.5 (58-72.25)	64 (58-72)
Male N (%)	29 (69)	35 (65)	64 (67)
Female N (%)	13 (31)	19 (35)	32 (33)

IQ –interquartile range

3.3.2 Baseline Comparison of Peri-Operative Factors

The randomised groups were compared for surgical and intraoperative factors i.e. type of surgical procedure, neo-adjuvant chemotherapy, intra-operative blood loss, duration of operation, ASA grade and POSSUM scores [612] . The results are presented in the following section and summarised in table 3.6 later in this section.

Neoadjuvant Chemotherapy

Thirty-six percent of the total study population received neo-adjuvant chemotherapy. The number of patients receiving neoadjuvant chemotherapy in the standard group was 18 (42.9%) and 18 (33.3%) in the enteral nutrition group. Despite the higher percentage in the standard group, the difference was not statistically significant.

Duration of Time in Theatre

There was no difference between the two groups for the mean duration of time spent in theatre. The standard group had a mean duration of 7.3 hours (SD 2.1 hours) and the early enteral nutrition group had a mean duration of 7.0 hours (SD 2.0 hours).

Intraoperative Blood Loss

There was no difference in intraoperative blood loss between the two randomised groups. The mean blood loss in the standard group was 1396 millilitres (SD 1195 mls) and 1168 millilitres for the enteral nutrition group (SD 672 mls).

American Society of Anaesthesiology (ASA) Grade

No statistical differences were identified between the two groups for ASA grade. From observing the data (table 3.6) it appears that more patients in the enteral nutrition group had a higher ASA grade when compared to the standard group, (59% versus 40.5%). As there was only one patient with an ASA grade of 1, the

statistical analysis was repeated excluding this patient. Once again the difference between the two groups was not statistically significant (Chi squared test p=0.098).

POSSUM Scores

The median POSSUM [612] scores were compared for the randomised groups. The results are presented in table 3.5. The groups were comparable for each predictive score.

Table 3.5 Median POSSUM scores for the two-randomisation groups at Baseline.

Possum Score	Physiology Median (IQ)	Operative Median (IQ)	Morbidity Median (IQ)	Mortality Median (IQ)	P-Mortality Median (IQ)
STD group	13 (12-15)	24 (20-24)	63.8 (52.8-67.8)	16.2 (11.6-20.1)	3.5 (2.6-4.8)
EEEN group	14 (12-15)	24 (24-24)	67.5 (63.8-74.1)	18.3 (16.3-22.3)	3.5 (2.7-4.9)

IQ = Interquartile range

P-Mortality is calculated using the Portsmouth POSSUM [572, 613]

To note, the predictive mortality from POSSUM for the sample population was between 16.2% for the STD group and 18.3% for the EEN group. This is higher than the predicted mortality from the P-POSSUM [572, 613], which is more in line with the reported mortality rates for UGI surgery from other centres [86, 132, 153, 154].

Summary of the Baseline Perioperative Risk Factors

In summary, no differences were highlighted between the two groups at baseline for surgical or intraoperative risk factors as outlined above. The results are summarised in table 3.6.

Table 3.6 Summary of Surgical Characteristics of the Two Randomised Groups at Baseline

	Standard Group	Enteral Group	Total Population
Pre-op Tumour stage I	4 (9.5)	5 (9)	9 (9.3)
N (%) II	18 (43)	26 (48)	45 (46.9)
III	19 (45)	21 (39)	39 (40.6)
IV	1 (2.5)	2 (4)	3 (3.2)
Pre-op Chemotherapy N (%)			
Yes	18 (42.9)	18 (33.3)	36 (36)
No	24 (57.1)	36 (66.6)	60 (64)
Tumour Diagnosis N (%)			
Oesophageal Cancer	21 (50)	24 (44.5)	45 (47)
Gastric Cancer	10 (23.8)	18 (33.3)	28 (29)
Pancreatic Cancer	11 (26.2)	12 (22.2)	23 (24)
Surgical Procedure N (%)			
Oesophagectomy	**21 (50)**	**24 (45)**	**45 (47)**
Transhiatal	7 (16.6)	10 (18.2)	17 (17)
Ivor Lewis	13 (31.0)	14 (25.5)	27 (29)
Three Stage	1(2.4)	0 (0)	1 (1.4)
Gastrectomy	**10 (24)**	**18 (33)**	**28 (29)**
Partial gastrectomy	1 (2.4)	1 (1.8)	2 (2.8)
Subtotal gastrectomy	5 (9.5)	8 (14.5)	13 (13.5)
Total gastrectomy	4 (9.5)	9 (16.4)	13 (13.5)
Pancreatic Resection	**11 (26)**	**12 (22)**	**23 (24)**
PPPD	9 (21.4)	8 (14.5)	17 (17.7)
Total pancreactectomy	2 (4.8)	4 (7.3)	6 (6.3)
Mean hrs theatre (SD)	7.3 (2.1)	7. 0 (2.0)	7.15 (2.0)
Mean Intraoperative Blood Loss mls mean (SD)	1395 (1195)	1167 (671)	-
Mortality Possum Score (IQ range)	16.2 (11.6-20.1)	18.3 (16.3-22.3)	-
ASA grade (%) 1	0 (0)	1 (2)	1 (1)
2	25 (59.5)	21 (39)	46 (48)
3	17 (40.5)	32 (59)	49 (51)

3.3.3 Baseline Comparison of Baseline Nutritional Parameters

All baseline nutritional parameters are presented in table 3.7. All baseline parameters for the two-randomisation groups were similar with no clinical or statistical differences between the two groups highlighted. The mean pre-illness BMI and mean pre-operative BMI are in the overweight category. However the percentage pre-operative weight loss is indicative of nutritional risk.

Table 3.7 Summary of the Baseline Mean nutritional Parameters of the Randomised Groups

	Standard Group N=42 Mean (SD)	**Enteral Nutrition N=54 Mean (SD)**
Mean pre-illness BMI	27.4 (4.2)	27.9 (5.06)
Mean pre-operative BMI	25.2 (4.1)	25.6 (5.4)
Mean pre-op % weight loss	7.2 (7.3)	6.8 (7.5)
Mean Nutritional risk Index	99.8 (11.33)	100.0 (10.88)
Mean pre-operative Weight (Kg)	73 kg	74kg
Calorie intake per day	1393 (415)	1508 (462)
Protein intake per day (grams)	58.1 (19.2)	57.8 (18.8)
^Equivalent Oral calorie intake/day/kg	19	20
^Equivalent Oral protein intake/day/g	0.8	0.8
Triceps skinfold thickness (mm)	13.6 (8.07)	13.03 (5.3)
Mid upper muscle circumference (mm)	30.7 (4.23)	30.41 (6.89)
Hand dynamometry (mmHg)	33.4 (10.4)	31.2 (11.2)

^ Calculated from calorie and protein intakes per day

Pre-operative Oral Food Intake

The mean calorie intake per day was 1393 calories per day (SD=415.6) for the standard group and 1508 calories per day (SD=462) for the enteral nutrition group. (This equated to 19 calorie per kg per day and 20 calorie per day respectively. Recommended calorie intake should be 30-35 kcals per kg/day [572].

The mean protein intake per day was 58.1 grams per day (SD 19.2 grams per day) for the standard group and 57.8 grams per day (SD 18.8 grams per day) for the enteral nutrition group. This equated to 0.79 grams per kilogram per day and 0.78 grams per kg respectively. The requirement is 1-1.5 grams protein/Kg/day [572].

Twenty six percent (N=11) of the standard group had a mean daily oral calorie intake of less than 1000kcals compared to 13% (N=7) in the enteral nutrition group (Table 3.8). The difference was not statistically significant. There was no difference for the protein intakes (table 3.8).

Table 3.8 Oral calorie intakes per day at Baseline.

Mean calorie intake/day	**Standard Group N (%)**	**Enteral Group N (%)**
Less than 600 kcals	1 (2.4)	2 (3.7)
601-999 kcals	10 (23.3)	5 (9.3)
1000 –1499 kcals	14 (33.3)	22 (40.7)
1500-1999 kcals	15 (35.7)	20 (37)
Mean protein intake/day		
Less than 20 g protein	1 (2.4)	1 (1.9)
21-35 g protein	3 (7.1)	7 (13)
36-50 g protein	13 (31)	15 (27.8)
51-65 g protein	11 (26.2)	13 (24.1)
66-80 g protein	8 (19)	11 (20.4)
More than 80 g protein	6 (14.3)	7 (13)

Of clinical relevance, all the patients (N=5) who developed peri-operative major complications within 48 hours that required a return to the operating theatre had protein intake of less than 0.48 grams per kilogram per day. This is a third of

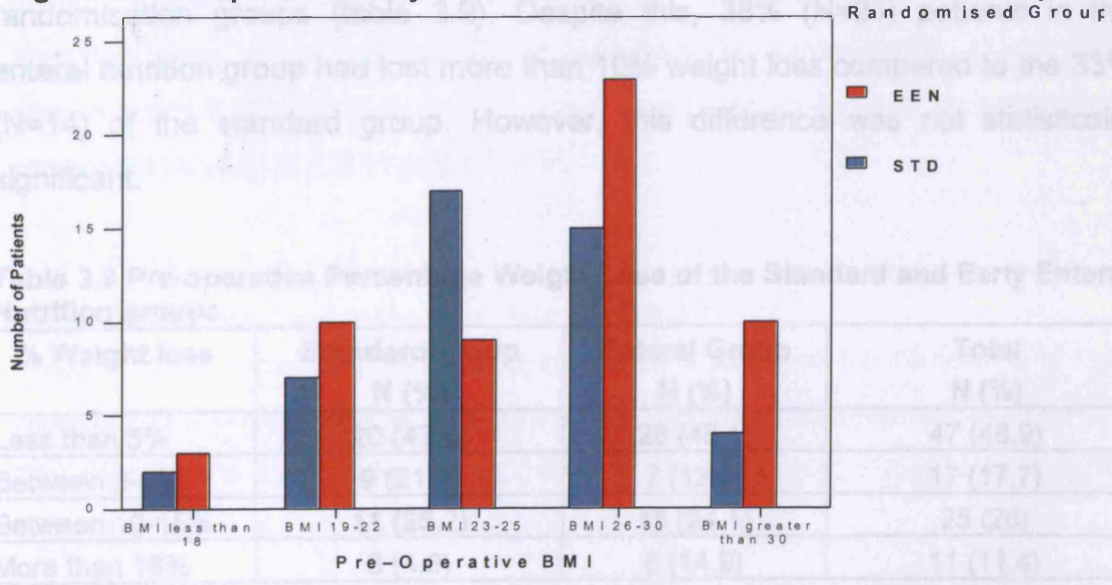
normal protein intake pre-operatively. All these patients reported a good appetite pre-operatively.

Pre-operative Body Mass Index (BMI)

The mean pre-illness Body Mass Index (BMI) for the total study population was 27.5. The mean pre-operative BMI remained in the overweight category for the total study population 25.4 (SD 4.8). Fifty-four percent of the total study population had a pre-operative BMI greater than 25 indicating that these patients are overweight. The incidence of obesity was 14.5 % in the total study population. Forty patients (41.6%) in the total study population had a BMI in the normal range i.e. 20-24. Five patients (5.2%) in the total study population had a BMI less than 18.

The mean BMI was similar for both randomised groups. More of the enteral nutrition groups, N=32 (59%), had BMI over 25 (i.e. the overweight category). This compared to 21 (50%) patients in the standard group. Ten patients (18.5%) in the enteral nutrition group compared to 4 (9.5%) in the standard group were morbidly obese pre-operatively.

Figure 3.3 Pre-operative Body Mass Index of the Two Randomisation Groups.



A relationship between BMI and surgical procedure was highlighted when the data were explored. Two oesophagectomy patients (4%), 7 (24%) gastrectomy patients (24%) and 3 (12%) pancreatic resection patients, had a BMI less than 19 (i.e. underweight). The results are presented in table III.I.I in appendix III. This suggests, that using BMI in patients undergoing gastrectomy were more undernourished pre-operatively using BMI, when compared to the other surgical procedures. Twenty patients (42%) undergoing oesophagectomy were overweight using BMI (BMI 25-30), compared to twelve (34%) gastrectomy patients and seven (28%) pancreatic patients. The incidence of morbid obesity (BMI greater than 30) was 19% - once again higher in patients undergoing oesophagectomy, compared to 14% in gastrectomy patients and 4% for pancreatic resection patients.

Percentage Weight Loss

The median percentage weight loss of the total study population was 6.3% (0.5-11%). Thirty-six patients (38%) in the total study population had lost more than 10% body weight in the 3 months prior to admission for surgery.

The median pre-operative percentage weight loss was similar for the two randomisation groups (table 3.9). Despite this, 38% (N=21) patients in the enteral nutrition group had lost more than 10% weight loss compared to the 33% (N=14) of the standard group. However, this difference was not statistically significant.

Table 3.9 Pre-operative Percentage Weight Loss of the Standard and Early Enteral Nutrition groups.

% Weight loss	Standard group N (%)	Enteral Group N (%)	Total N (%)
Less than 5%	20 (47.6)	26 (48.1)	47 (48.9)
Between 6-9%	9 (21.4)	7 (13.0)	17 (17.7)
Between 10-15%	11 (26.2)	13 (24.1)	25 (26)
More than 16%	3 (4.8)	8 (14.9)	11 (11.4)

A relationship between percentage weight loss and gender was identified when the data were explored. The median percentage weight loss for males was 4.5% (0-10.6)) and for females was 9.2% (0.6-12.3). (This was not statistically different U=889; p=0.114). The results are presented in table III.I.II appendix III. Twenty-five men (17%) compared to 21 women (65%) had lost more than 10% weight loss prior to admission in the previous 3 months. As with BMI, patients undergoing gastrectomy lost the greatest percentage weight with 62% (N=8) of the patients losing more than 10% weight loss pre-operatively.

Nutrition Risk Index

Patients were comparable at baseline for degree of malnutrition using the Nutrition Risk Index (NRI). The majority of patients in both groups were classified as borderline using the NRI (table 3.10).

Table 3.10 A comparison of Pre-operative Nutrition Risk Index Score between the two randomised groups

NRI	Standard group		Enteral Group	
	N	%	N	%
Severe PEM	4	10	6	12.5
Moderate PEM	4	10	2	4.2
Borderline PEM	32	80	40	83.3

Females were more nutritionally at risk prior to surgery with 21.4% (N=6) compared to 6.7% (N=4) males having a severe score for NRI. The results are presented in table III.I.III in appendix III.

Appetite and Pre-operative Oral Food Intake

Patients were asked to rank their appetite on a scale of 1-5 compared to usual appetite. The results for the two randomised groups are presented in table 3.11. This measure is subjective, but 'appetite' is an often-used clinical term and was deemed important to collect for the purpose of the trial.

The median appetite scores were similar for the two randomised groups 4 (IQ range 2-4) and 4 (IQ range 3-4) respectively for the standard groups and for the early enteral nutrition group. Twenty one percent of the enteral nutrition group had a reduced appetite compared to 31.7% of the standard group.

Table 3.11 Appetite Scores for the Two Groups

Appetite Score	Standard Group N (%)	Enteral Group N (%)	Total N (%)
1 (very poor)	3 (7)	5 (9)	8 (8.3)
2 (reduced)	10 (24)	6 (11)	16 (16.6)
3 (average)	8 (19)	11 (21)	19 (20)
4 (good)	14 (33)	21 (39)	35 (36.4)
5 (excellent)	7 (17)	11 (20)	18 (18.7)

Hand Grip Dynamometry

Handgrip dynamometry was compared at baseline for the two randomised groups (table 3.12). The mean handgrip dynamometry for the standard groups was 33.4mmHg and 30.9 mmHg for the enteral nutrition group.

Table 3.12 Comparison of the Randomisation groups for Pre-Operative Handdynanometry expressed as 85% of normal.

Handdynanometry less than 85% of normal	Standard Group N (%)	Enteral group N (%)	Test Statistic (p)
Yes	18 (42)	23 (44)	NS
No	19 (45)	22 (41)	
Missing data	5 (13)	9 (15)	

Factors that have an Impact on Oral Food Intake

Comparisons at baseline of the factors that affect oral intake were made. The results are presented in table 3.13. The groups were similarly matched for all factors. The incidence of dysphagia was 18.8% for the study population. The incidence of diabetes (both Type I and II) was 47% for the total study population.

Table 3.13 Symptoms affecting food intake a comparison of randomised groups

Did the patient report and of the symptoms listed below?	**Standard group N=42 N (%)**	**Enteral Nutrition group N=54 N (%)**	**Total Study Population**
Dysphagia			
Yes	9 (21)	9 (17)	18 (18.8)
No	33 (79)	45 (83)	78 (82)
Nausea			
Yes	14 (33)	13 (24)	27 (28)
No	28 (67)	41 (76)	69 (72)
Vomiting			
Yes	14 (33)	11 (20)	25 (27)
No	28 (67)	42 (80)	70 (73)
Taste Changes			
Yes	10 (23)	9 (17)	19 9 (20)
No	32 (77)	45 (83)	77 (80)
Chewing Problems			
Yes	2 (5)	0 (0)	2 (2)
No	39 (95)	49 (100)	88 (98)
Bowel problems			
Yes	13 (31)	16 (30)	29 (31)
No	29 (69)	38 (70)	67 (69)

3.3.4 Baseline Comparison of Biochemical Parameters

The baseline biochemical parameters were comparable for the two-randomisation groups. The results are presented in table III.I.IV in appendix III. All mean parameters were in the normal clinical reference range at baseline.

3.4 Group Allocation and Equivalence

The chapter has so far explored the data from the two-randomisation groups at baseline prior to any study intervention. The baseline data from the SF-36 Health Related Quality of Life is presented later in this chapter.

No differences were found between the randomised groups for operative, demographic and nutritional characteristics. The standard group and enteral nutrition group were therefore considered suitable for the purpose of statistical analysis in the analyses of the primary and secondary outcomes.

3.5 Analysis of Primary Outcome

The primary outcome for the MCRCT was a comparison of the length of hospital stay (LOHS) in days by group. This section will present the results of the analysis of LOHS.

3.5.1 Intention-to-Treat Analysis

The results of the intention-to-treat analysis concluded that the median length of hospital stay for the STD group was 20 days (IQ range 14.75-28) compared to 16 days (IQ range 13-22.75) for the EEN group. The difference between the groups was approaching statistical significance (U=999.70 p=0.65). The data was not normally distributed.

3.5.2 Per Protocol Analysis

In addition to the Intention-to-treat analysis a per-protocol analysis was also performed. Six patients were excluded for this analysis for the following reasons:

1. The need to return to theatre due to major complications within 24-48 hours post-theatre (N 3)

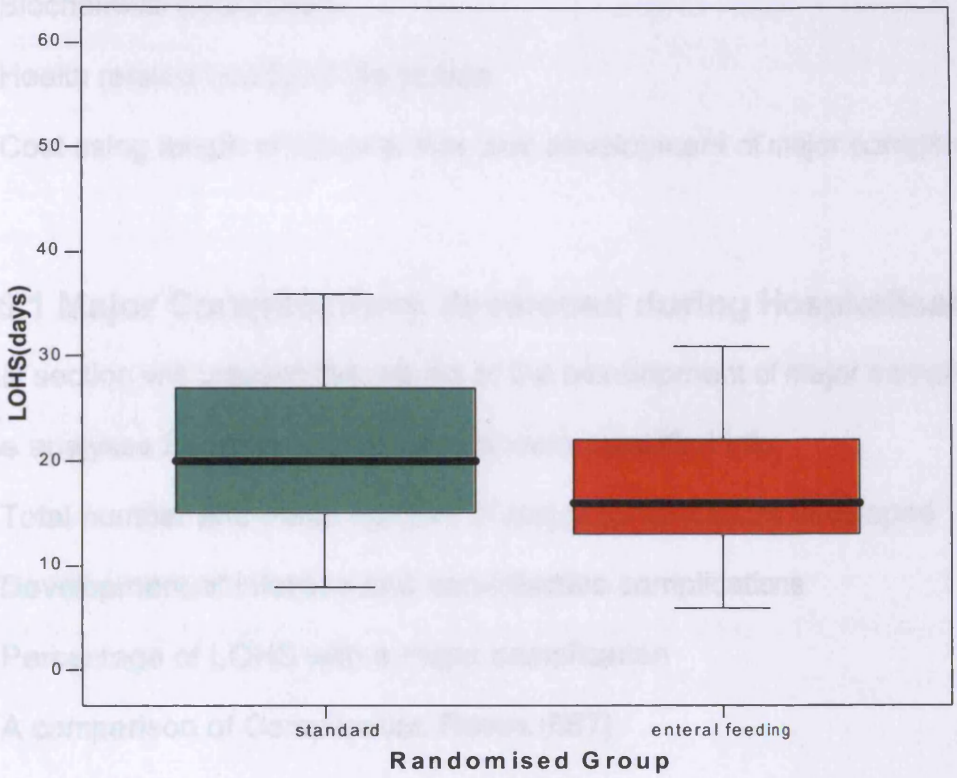
2. Died within 24-48 hours post-operatively (N=1)

3. Had a nasojejunal tube (N=2)

All the events leading to withdrawal were unrelated to enteral feeding, as they all occurred prior to the commencement of the enteral feed.

The results of the per-protocol analysis indicated that the median LOHS for the STD group was 20 days (IQ range 14.75-28 days) compared to 16 days (IQ range 13-22 days) in the EEN group (figure 3.4). The difference between the groups was statistically significant (U=822.50, p=0.021). The data were not normally distributed as illustrated by the QQ plot (figure III.II.I in appendix III.II). The results indicate that the null hypothesis of the MCRCT can be refuted.

Figure 3.4 Length of hospital stay and inter-quartile ranges of the two randomised groups-Per Protocol Analysis



There were five outliers in the per-protocol analysis of the primary outcome. Three outliers in the STD group and two in the EEN group; all had LOHS exceeding 40 days. These prolonged LOHS are attributed to the development of major complications.

3.6 Analysis of Secondary Outcomes

The MCRCT had multiple secondary outcomes. This section will present the results of the comparisons of the secondary outcomes, between the two randomised groups. All analyses are on a per-protocol analysis basis. Results will be presented for the differences in the:

1. Development of major complications
2. Readmission rates at 6 and 12 weeks post-discharge.
3. Development of minor complications
4. Fluid balance and prescription of intravenous fluids.

5. Nutritional parameters

6. Biochemical parameters

7. Health related quality of life scores

8. Cost using length of hospital stay and development of major complications

3.6.1 Major Complications developed during Hospitalisation

This section will present the results of the development of major complications.

The analyses for major complications were classified into:

1. Total number and mean number of major complications developed

2. Development of infective and non-infective complications

3. Percentage of LOHS with a major complication

4. A comparison of Complication Ratios [567]

5. Difference in number of major complications on discharge

Total Number of Major Complications Developed Between the Two Randomised Groups

The STD group (N=42) had a total of 69 major complications compared to 26 in the EEN group (N=54). The mean number of major complications developed per group was 1.64 (SD 1.88) for the STD group and 0.54 (SD1.0) for the EEN group (t=3.49; p=0.001). This suggests that the STD group developed 3 times as many major complications than the EEN group on average.

More patients in the EEN group had an uncomplicated post-operative recovery, when compared to the STD group (68.8% versus 39%). Similarly, ten patients (25%) in the STD group versus 1 patient (2.1%) in the EEN group developed more than 4 major complications post-operatively. The results are presented in table 3.14.

Table 3.14 Total Number of Major Complications developed Post-operatively by Randomised Group

Total no. of major complications	STD group N (%)	EEN Group N (%)	Total Study Group
0	14 (34.2)	35 (66.0)	49
1	13 (31.8)	11 (20.0)	24
2	1 (2.4)	4 (7.5)	5
3	3 (7.3)	2 (4.6)	5
4	6 (14.6)	1 (1.9)	7
5	3 (7.3)	0 (0)	3
6	1 (2.4)	0 (0)	1
Total	41* (100)	53* (100)	94

*There were two peri-operative deaths one in each group

The Classification of Major Complications

The major complications results are presented in table 3.15. More patients in the STD group 28.5% (N=12) developed wound infections compared to the EEN group 5.5 % (N=3) (chi square=16.3, p<0.0001). Likewise, the standard group developed more chest infections 21.4% (N=9) versus 9.3% (N=5) in the enteral nutrition group (chi squared=6.03; p=0.05). The incidence of pleural effusion was similar for both groups.

There were differences in wound healing between the two groups. This was manifested by a reduction in open abdominal wounds and anastomotic leaks in the EEN group. Four patients (9.5%) in the STD group compared to one patient (1.9%) in the EEN group had an abdominal wound breakdown. This did not reach statistical significance.

For anastomotic leaks, 16.6% (N=7) of the STD group compared to 1.8% (N=1) in the EEN group developed a leak (chi squared=6.73; p=0.01). The development of anastomotic leaks occurred irrespective of the type of surgical procedure. Three patients with anastomotic leak had oesophagectomies, 2 patients had gastrectomies and 2 patients had PPPD.

The incidence of respiratory failure (STD 6% versus EEN 2.3%) and chylothorax (STD 2.1% versus EEN 0%) was higher in the EEN group. The results were not

statistically significant. However, the numbers in each group are too small for reliable comparison.

Delayed gastric emptying occurred in patients who had pancreatic resection. More patients in the STD group 7.3% (N=3) versus 1.8% (N=1) in the EEN group developed delayed gastric empting. The differences with delayed gastric emptying should be interpreted with caution as the numbers for comparison are small, but it does refute one study [424] that concluded continuous enteral feeding via a needle catheter jejunostomy decreased gastric emptying in patients undergoing pancreatic resection.

Patients in the EEN group had fewer urinary tract infections (2.1% versus 7.3%; NS); fewer haemorrhages (0% versus 2%); and less myocardial infarction (0% versus 2.3%). However, caution is again advised when interpreting these findings, as the number of patients in each subgroup is very small.

Table 3.15 Percentage and Number of Major Complications by Randomised Group

Type of Complication	STD Group % (N)	EEN Group % (N)	Chi squared test (p)
Infective Complications			
Wound Infection	28.5 (12)	5.5 (3)	16.3 (0.0001)
Chest Infection	21.4 (9)	9.3 (5)	6.025 (<0.05)
Urinary Tract Infection	7.3 (3)	2.1 (1)	1.92 (0.38)
Septicaemia	0 (0)	0 (0)	-
Non Infective Complications			
Delayed Gastric Emptying	7.3 (3)	1.8 (1)	3.95 (0.11)
Myocardial Infarction	2.3 (1)	0 (0)	2.61 (0.41)
Major Haemorrhage	4.9 (2)	0 (0)	3.23 (0.17)
Pleural effusion	17.1(7)	14.3 (7)	0.78 (0.84)
Chylothorax	0 (0)	2.1 (1)	2.29 (0.53)
Anastomotic Leak	16.6 (7)	1.8 (1)	6.73 (0.01)
Open abdominal wounds	9.5 (4)	1.9 (1)	2.78 (0.18)
CVA	0 (0)	0(0)	-
ARDS	0 (0)	0 (0)	-
Respiratory Failure	2.3 (1)	11.1 (6)	0.85 (0.34)
Mortality Rate (30 day)	2.3 (1)	1.9 (1)	-
Total complications	**49**	**26**	

Percentage of Length of Hospital Stay spent with Complications

The next section will compare the two groups for the proportion of their LOHS spent with a major complication. The results are presented in table 3.16.

Thirteen patients (34%) in the STD group spent more than half their post-operative stay with a major complication compared to 3 patients (6.3%) in the enteral nutrition group. The results once again indicate that EN reduces the time post-operatively spent with a major complication as compared to the STD group.

Table 3.16 Length of Time with a Major Complication as a Percentage of Hospital Stay

Percentage of LOHS with a major complication	STD Group N (%)	EEN Group N (%)
0%	14 (34.2)	35 (66.0)
1-10%	4 (9.8)	9 (16.9)
11-20%	4 (9.8)	4 (7.5)
21-30%	1 (2.4)	1 (1.9)
31-40%	4 (9.8)	1 (1.9)
41-50%	1 (2.4)	0 (0)
More than 51%	13 (31.6)	3 (5.8)
Total patients (missing data)	41 (1*)	53 (1*)

* 2 peri-operative deaths one from each group

Complication Ratios

A study by McAleese and Oldling-Smee (1994) [567] determined complication ratios for major complications (see methods section). These ratios can be applied to length of hospital stay in surgical patients to establish how each major complication will increase LOHS.

Complication Ratio=

Mean* LOHS stay with complication / Mean* LOHS stay without complications

*The mean LOHS was used for this calculation as proposed by the authors [567]

For the purpose of this study, a comparison of enteral nutrition and standard management on the complication ratios was calculated. The results are presented in table 3.17.

The results suggest that the presence of any major complication increased LOHS by 1.47 times for the total study population. By using early enteral feeding post-operatively the complication ratio was 1.39 versus 1.55 for standard management.

Complication ratios for each major complication were calculated (table 3.17). The STD group tended to have higher complication ratios as compared to the EEN group, indicating that EN reduces the severity of major complications and hence reduces LOHS.

Table 3.17 A Comparison of Complication Ratios* McAleese and Oldling-Smee by randomisation groups

Type of Complication	STD Group Mean ratio (LOHS)	EEEN Group Mean ratio (LOHS)	Total Group Mean ratio (LOHS)
All Major Complications	1.55 (24.18;)	1.39 (20.19)	1.47 (22.2)
Infective Complications	1.50 (23.46)	1.28 (18.6)	1.45 (21.9)
Wound Infection	1.66 (25.9)	1.14 (16.6)	1.39 (20.9)
Chest Infection	1.33 (20.8)	1.42 (20.6)	1.51 (22.7)
Non Infective Complications	1.35 (21.1)	1.29 (18.7)	1.32 (19.9)
Delayed Gastric Emptying	1.41 (22.1)	1.28 (18.6)	1.35 (20.3)
Pleural effusion	1.81(28.3)	1.66 (24.1)	1.75 (26.4)
Chylothorax	- (-)	1.4** (20.3)	1.4 (21.1)
Anastomotic Leak	1.9 (29.7)	- (-)	1.9 (28.7)
Open abdominal wound	1.38 (21.6)	2.45** (35.6)	1.55 (23.4)
Respiratory Failure	1.6 (25.0)	0.96 (28.5)	1.22 (18.4)

*This is the predicted LOHS for each complication based on the actual LOHS for each randomisation group (standard group=15.64 days (7.4); enteral group=14.53 days (5.13) total study population = 15.08 days).
**Interpret with caution, n=1.

The results suggest that the development of a wound infection in the STD group will increase LOHS by 1.66 times; pleural effusion by 1.81 times and an anastomotic leak 1.9 times. The mean LOHS for the STD group patients who developed no post-operative complications was 15.64 days (SD 7.4 days). Therefore, the corresponding LOHS for each of the major complications developed would be 25.9 days for wound infection, 28.30 days for pleural effusion and 29.7 days for anastomotic leak.

The calculation of complication ratios in the EEN group, suggests that the increase in LOHS if a patient developed a wound infection was 1.14 and 1.66 for a pleural effusion. No comparison can be made for this MCRCT for patients with

anastomotic leak as no patient in the EEN group developed one. The mean LOHS for the EEN group who developed no post-operative complications was 14.53 days (SD 5.13 days). Therefore, the corresponding increased LOHS will be 17.7 days (range 10.72-22.41 days) for wound infection. For pleural effusion the LOHS would be 24.1 days (range 15.6-32.6 days).

The conclusions to be drawn so far from this early analysis are that if a patient develops a major complications, enteral nutrition may reduce LOHS by 16.5% for all major complications, may reduce LOHS by 20.7% for infective complications and may reduce LOHS by 11.1% for non-infective complications.

The EEN group however, had a higher complication ratio for chest infection, abdominal wound breakdown and chylothorax. The number of patients in the EEN group with abdominal wound breakdown and chylothorax was only one and consequently caution needs to be used when interpreting these results.

The authors [567] suggest that the complication ratio may also reflect the severity of major complications. According to the results of this RCT, the most severely impacting complications were pleural effusion, anastomotic leak and chylothorax. This was based on the complication ratios of the total study population.

3.6.2 Presence of Complications on Day of Discharge

The presence and type of complications on the day of discharge were compared (table 3.18). Six patients (11.1%) in the EEN group reported complications on the day of discharge, compared to 14 patients (33.3%) in the STD group (Chi square= 8.56; p=0.0001).

Table 3.18 Types and frequency of Major Complications on Discharge

Group	Developed no Complications N (%)	Chest N (%)	Wound N (%)	Anastomotic Leak N (%)	Other * N (%)	Missing data N (%)
STD	25 (59.5)	1 (2.3)	10(23.8)	3 (7.1)	2 (4.7)	1 (2.3)
EEN	48 (88.8)	0(0)	3(5.5)	0(0)	3 (5.5)	2 (1.9)

*Other= oedema, dysphagia secondary to vocal cord palsy, severe anorexia

3.6.3 Hospital Readmissions Rates

Patients were reviewed at 6 weeks and 12 weeks post discharge. Only readmissions related to the initial surgical procedure were recorded. Data were only recorded if the patient required a minimum of one night inpatients stay. The results of readmissions within the first 6 weeks after discharge are presented in table 3.19.

Six patients (14.3%) in the STD group required readmission within 6 weeks compared to 4 patients (7.6%) of the EEN group. The difference was not statistically significant.

Table 3.19 Readmission Rates between discharge and 6 Weeks by Randomisation Group

Readmission between discharge and 6 weeks	Standard Group N (%)	Enteral Group N (%)	Chi square
Yes	6 (14.3)	4 (7.6)	NS
No	36 (85.7)	48 (92.4)	
Total	42	52*	

* missing data N=2

Two patients (4.8%) in the STD group compared to 1 patient (1.9%) in the EEN group required readmission at 12 weeks post discharge (table 3.20). The difference was once again not statistically significant.

Table 3.20 Readmission Rates between 6 weeks and 12 weeks by Randomisation Group

Readmissions between 6 weeks and 12 weeks	STD Group N (%)	EEN Group N (%)	Chi square
Yes	2 (4.8)	1 (1.9)	NS
No	40 (95.2)	51 (98.1)	
Total	42	52*	

missing data N=2

3.6.4 Tolerance and Feasibility of Enteral Nutrition

This section will present the data regarding the tolerance and feasibility of enteral nutrition delivered in the immediate post-operative phase.

All results are comparisons between the two randomised groups unless otherwise specified.

Complications related to the Needle Catheter Jejunostomy

There were no reported complications associated with infection at the catheter site, leakage from the catheter or displacement of the catheter. There were no reported major jejunostomy related complications for the total study population.

There were two tubes blockages, one in either group. Neither of the blockages caused cessation of either enteral feed or water for more than 4 hours.

Volume of Enteral Feed Delivered

All EEN group patients commenced enteral feeding within 24 hours of their surgical procedure. The number of patients in the EEN group who had uninterrupted enteral feeding in the 1st week was 85.2% (N=46). The mean daily volumes of enteral feed delivered are presented in table 3.21.

Enteral nutrition was delivered to eight patients in the STD group within the first 7 days post-operatively. The reasons for this are presented in table 3.23. All patients in the STD group who received EN were fed as per EEN group protocol. However, the mean volume of enteral feed delivered to the STD group did not exceed a mean volume greater than 95 mls/day (SD 242-458 mls) and 9.6% of their nutritional requirements for the 1st 7 days post-operatively. All patients were analysed on an intention to treat basis.

Table 3.21 Mean volume of enteral nutrition delivered per day (millilitres)

Post operative Day	EEN Group Mean vol. (SD)	STD Group Mean vol. (SD)	ANOVA
1	317(172)	0 (0)	$F_{1, 95}$=125.4 (p>0.0001)
2	615 (283)	0 (0)	
3	946 (389)	0 (0)	
4	1168 (577)	65 (242)	
5	1294 (655)	45 (366)	
6	1296 (747)	95 (458)	
7	1450 (682)	244 (547)	

The mean volumes of EN delivered in the STD group are for all patients in the STD group and not the mean volumes for the patients who received EN.

The volume of EN and the percentage of nutritional requirements achieved by the EN varied each day. From the table 3.22 it can be seen that the maximum percentage of nutritional requirements achieved by the EEN group was 71.2% (SD 124.7%) occurring on day 4 post-operatively. 100% of nutritional requirements were achieved by some of the EEN group as indicated by the standard deviations.

Table 3.22 Mean (SD) Percentage of Nutritional requirements delivered per day

Post-operative Day	STD Group N=42 Mean % Nutritional Requirements (SD)	EEN Group N=46 Mean % Nutritional Requirements (SD)
1	0 (0)	13.6 (10)
2	0 (0)	29 (19)
3	0 (0)	44 (24.2)
4	3.9 (14.1)	71.2 (124.7)
5	2.5 (14.2)	59.8 (32.6)
6	5.5 (23.4)	59.8 (31.7)
7	9.6 (28.3)	63.2 (31.1)

A summary of the delivery of enteral nutrition is presented in table 3.26. The mean time post-operatively that the enteral nutrition was commenced at was 12.3 hours (SD 6.2 hours).

The mean rate of commencing the enteral nutrition was 17.92 mls/hour (SD 9.06) on day 1. The protocol advised that patients were commenced at 20 mls/hour, in

line with the study feeding protocol. The variation is due to nursing documentation at ward level.

The rate of feed delivery on day 3 was 46.1 mls/hour (SD 16.7mls). The mean is in line with the protocol, but the standard deviation suggests that some patients were receiving enteral nutrition at a greater rate. The rate of feed on day 5 was 57.9 mls/hour (SD 25.43). This is in line with the feed protocol.

By day 7, the rate of feed was 61.5 ml/hour (SD 26.8mls). This is the day the patients often had their gastrograffin swallows and hence the enteral nutrition would have been discontinued temporarily.

The mean number of days post-operatively that the EEN group received enteral nutrition was 12.4 days (SD 6.33 days). There was variation in the length of time the EEN group received the enteral nutrition, with two patients stopping on day 6 (as they were ready for discharge) and one patient who was fed for 41 days (secondary to vocal cord palsy and dysphagia). This patient was subsequently discharged home with enteral feeding.

Table 3.26 Summary of the delivery of enteral nutrition

Variable	STD Group Mls/day	EEN Group Mls/day
Mean hours post op enteral nutrition commenced (SD)	N/A	12.3 (6.2)
Rate feed commenced mls (SD)	11.50 (water)	17.92 (9.06)
Volume of feed delivered day 3 mls (SD)/day	50.71 (37.0)	959.9 (381.0)
Rate of feed day3 mls (SD)	9.8 (1.5)	46.1 (16.7)
Volume of feed delivered day 5 mls (SD)/day	51.4 (234.3)	1333.8 (656.4)
Rate of feed delivered day 5 mls (SD)	12.1 (98)	57.9 (25.43)
Volume of feed delivered day 7 mls (SD)/day	229.7 (512)	1433.7 (702.44)
Rate of feed day 7 Mls (SD)	7.8 (20.6)	61.5 (26.8)
No. of days enteral feed delivered	N/A	12.4 (6.33) range 6-40 days
Mean day post-op enteral nutrition stopped	N/A	13.7 (16.3) range 6-41 days

Reasons why the Standard Group Commenced Enteral Feeding in the Early Post-Operative Period

A total number of 8 (19%) patients commenced EN in the STD group by seven days post-operatively. The reasons are given in table 3.23.

Two patients on day 4 commenced enteral feeding due to surgeon preference. One patient commenced enteral nutrition due to a suspected chest complication.

By day 7, three patients were commenced on EN due to anorexia and oedema. One patient commenced EN due to a suspected anastomotic leak.

Table 3.23 Number of Standard Group Patients who received Enteral Nutrition post-operatively and the Reasons for starting

Operation Type	Centre	Day feed started	Reason	Feed type	No. Of days feed	Day oral diet commenced	LOHS
IL	1	4	Surgeon request	Peptisorb	47	8	51
IL	1	4	Surgeon request	Perative	20	14	26
Trans	1	4	? Chest infection	Osmolite	14	15	20
IL	1	5	Chest complication	Osmolite	12	13	20
PPPD	1	7	Oedema/anorexia	Perative	23	12	35
Transhiatal	1	7	Oedema/anorexia	Osmolite	15	11	18
Transhiatal	1	7	Oedema/anorexia	Perative	11	13	15
IL	1	7	Anastomotic leak	Osmolite	27	20	35

IL- Ivor Lewis oesophagectomy, ? –suspected , LOHS- length of hospital stay; PPPD Pylorus preserving pancreaticoduodenectomy; Transhiatal=transhiatal oesophagectomy

Table 3.24 Summary of the reasons why enteral nutrition was commenced in the standard group

Reasons for Enteral Nutrition	Day 4	Day 5	Day 6	Day 7	Day 9	Day 12
Clinical Error	0	0	0	0	0	0
Surgeon preference	2	2	2	2	3	3
Major complication	1	2	2	3	8	20
Minor Complication	0	0	0	3	3	1
Receiving enteral nutrition/day N (%)	3 (7.1)	4 (16.6)	4 (16.6)	8 (19)	14 (24)	20(48)

Reasons for Stopping Enteral Nutrition in the Enteral Nutrition Group

The number of patients who needed to have their enteral nutrition stopped or interrupted in the 1st post-operative week was 16% (N=9). The reasons are outlined in table 3.25.

Table 3.25 Reasons for Interrupting Enteral Nutrition delivery in the Enteral Nutrition Group

Operation type	Centre	Day feed stopped	Reason	Action	No. Of days feed stopped	Day enteral feed resumed	LOHS
IL	1	3	Chylothorax	TPN	25	28	50
Gastric	1	5	? chest Infection	NBM	1	6	11
Gastric	1	4	Oozing wound	NBM	2	6	7
Gastric	1	7	Abdominal pain	NBM	Not resumed	N/A	16
Gastric	1	5	? chest infection	NBM	1	6	16
Gastric	2	6	? chest infection	NBM	Not resumed	N/A	13
Gastric	2	6	? chest infection	NBM	1	7	16
Gastric	1	5	? chest infection	NBM	1	6	14
PPPD	1	5	? anastomotic leak	NBM	1	6	17

IL=Ivor Lewis oesophagectomy, PPPD= pylorus preserving pancreaticoduodenectomy, TPN=total parenteral nutrition, NBM= nil by mouth, ? suspected diagnosis, N/A not applicable

Number of Patients receiving Enteral Nutrition on the Day of Discharge

On the day of discharge, 6 patients (14.2%) in the STD group were requiring enteral nutrition and were subsequently discharged home on enteral nutrition. In comparison 1 patient (1.8%) of the EEN group were discharged home on enteral feeding.

Table 3.27 Number of patients requiring Home Enteral Nutrition

Type of feed required on discharge	Standard Group N (%)	Enteral nutrition group N (%)
No Feed	36 (86)	53 (98.2)
Water	0 (0)	0 (100)
Whole Protein	4 (9.5)	1 (1.8)
Semi-elemental	2 (4.7)	0 (100)
Missing	0 (0)	0 (0)

The reasons for patients being discharged on home enteral nutrition are presented in table 3.28. Fifty percent of the STD group requiring home enteral nutrition remained nil by mouth post-discharge. The one patient in the enteral group requiring home enteral nutrition had vocal cord palsy and dysphagia.

Table 3.28 Patients discharged on Home Enteral Nutrition.

Patient ID	Randomisation group	Reason for HEF	Nil by mouth?
43	Standard	Anastomotic leak	Yes
47	Standard	Anastomotic leak	Yes
81	Standard	Anastomotic leak	Yes
23	Standard	Wound infection/poor appetite	No
14	Standard	Wound Infection/poor appetite	No
3	Standard	Poor appetite	No
53	Enteral nutrition	Dysphagia	Yes

3.6.5 Development of Minor Complications Post-operatively

The section will present the minor complications developed in the post-operative period by randomisation group. Differences in nausea and vomiting, nasogastric aspirates, abdominal distension, bowel function and pain will be presented.

Nausea and Vomiting

The incidence of nausea and vomiting in the 1st seven days post-operatively was analysed (table 3.29).

Fifteen patients (35.7%) in the standard group reported at least one episode of nausea in the 1st 7 post-operative days, compared to 15 (27.3%) in the enterally fed group (Chi square=8.82; p=0.06)

Vomiting in the first week occurred in 10 patients (23.8%) in the STD group and 8 patients (14.5%) in the EEN group (Chi square=10.89; df 4 p=0.01)

Table 3.29 Number of patients reporting nausea and vomiting in the first week post-operatively

Presence of nausea in 1st week	**STD group N (%)**	**EEN Group N (%)**	**Chi square *(p)**
Yes	15 (35)	15 (27.3)	8.82,
No	26 (62)	39 (70.9)	(0.06)
Presence of Vomiting in 1st week			
Yes	10 (23.8)	8 (14.5)	10.88, (0.01)
No	31 (73.8)	46 (83.6)	

*** Fischer exact test**

Nasogastric (NG) Aspirates

NG aspirates are frequently used in clinical practice to reflect gastrointestinal motility post-operatively. High NG aspirates are thought to reflect delayed gastric emptying and altered small bowel motility. Daily NG aspirates were recorded and the median daily results per randomised group are presented in table 3.30.

Table 3.30 Nasogastric Aspirates in millilitres (mls) by Randomised groups

Day post op	STD group N (missing)*	STD NG asps mls median (IQ range)	EEN group N (missing)*	EEN NG asps mls median (IQ range)	U
1	42 (0)	205 (0-375)	54 (0)	200 (0-601)	NS
2	36 (6)	127 (0-445)	44 (10)	375 (163-325)	NS
3	37 (5)	212 (0-685)	50 (4)	0 (0-375)	p=0.081
4	38 (4)	200 (0-650)	47 (7)	0 (0-200)	NS
5	37 (5)	79 (0-510)	45 (9)	0 (0-336)	NS
6	37 (5)	0 (0-370)	46 (8)	0 (0-362)	NS
7	36 (6)	0 (0-494)	49 (5)	0 (0-182)	NS

**** number of missing patients, data not available on wards/recorded.***

There was no statistically significant difference between median volumes of NG aspirates reported between the two groups. On day 3 the difference in median volumes was approaching significance (p=0.08) with the standard group having more NG aspirates than the enteral nutrition group.

Abdominal Distension

The development of abdominal distension is a side effect often reported with the early use of EN. The incidence of abdominal distension for the total study population was 12.5% (N=12). The presence of abdominal distension peaked on day 3-4 post-operatively for both groups. There were no differences reported between the groups in incidence of abdominal distension. The percentage of patients in the STD group that reported abdominal distension for the first 7 days post-operatively was 14.3% (N=6), for the EEN group 11.1% (N=6) patients reported abdominal distension.

Bowel Function

Bowel function i.e. passage of flatus and stools are often considered by surgeons to be vital clinical stages in the post-operative recovery of surgical patients. However, as outlined in section 1.5.1.5 these do not reflect resumption of bowel function post-operatively.

The use of Ultrasound to Determine Return Of Peristalsis Post-operatively

As outlined in section 2.1.6.2 the use of ultrasound imaging (USS) at the bedside to detect the number of peristaltic waves in the small intestines was developed. The results are presented below.

A subgroup of consecutive patients (N=25) had their motility determined using USS (section 2.1.6.2). These patients were consecutively admitted from November 2002 to May 2003. The results are presented in table 3.31.

Table 3.31 Number of peristaltic waves/minute in the small intestines post-operatively as determined using Ultrasound Imaging

Post op day	STD group Mean (SD)	EEN group Mean (SD)	T test (p)
4	4.8 (2.6)	13.9 (2.01)	-4.039 (0.0001)
5	5.33 (2.08)	12.6 (5.3)	-2.26 (0.050)
6	9.2 (1.72)	14.17 (6.6)	NS

From the table the results indicate that the EEN group had more peristaltic waves per minute on day 4, day 5 and day 6 post-operatively. The difference between the groups reached statistical significance on days 4 and 5. The mean frequency of waves for the EEN group was 13.9 (SD 2.01) on day 4 and this remained similar for days 5 and day 6 post-operatively. The mean frequency for the standard group gradually increased over days 4-6. However, the mean frequency never achieved the score of the EEN group.

Passage of Flatus

The results from this MCRCT suggest an earlier passage of flatus in the EEN group compared to the STD group, with 20% (N=11) of the EEN group versus 2.3% (N=1) passing flatus by day 4 post-operatively (Chi square=25.5; p=0.0001). The results need to be interpreted with caution as several patients reported passage of flatus after passing stools suggesting under-reporting of passage of flatus.

Passage of Stools

Comparison of the groups on day 4, suggests that EEN stimulated patients to pass stools quicker than STD management. Eight patients (97.7%) in the EEN group had opened their bowels compared to 1 patient (2.3%) in the STD group on day 4 post-operatively (Chi square=20.49; p=0.0001). Fourteen patients (26.4%) in the EEN group opened their bowels on day 5 post-operatively compared to 2 patients (4.7%) of the STD group (Chi square=17.47; p=0.001). By day 7, forty-two patients (61.3%) in the EEN group had opened their bowels compared to 11 patients (25.8%) in the STD group (Chi square =19.54; p=0.001). A summary of the results of patients who opened their bowels, in the first week post-operative for the two randomised groups are presented in table 3.32.

Table 3.32 Number of Patients who reported Bowels opened in 1st week Post-Operatively

Bowels opened in 1st week post-op	No. Of patients (%)
Standard Group	
Yes	20 (46.5)
No	22 (53.5)
Enteral Group	
Yes	32 (59.3)
No	21 (38.7)

Incidence of Diarrhoea

The incidence of diarrhoea in the 1st week was reported in 12 (12.5%) patients in the total study population. The incidence of diarrhoea in the 1st week was 14% (N=6) for the STD group and 11.1% (N=6) for the EEN group. The difference was not statistically significant. The results are presented in table 3.33.

Table 3.33 Number of patients reporting diarrhoea by randomised group in the first 7 days

Diarrhoea reported in 1st week post-op ?	No. of patients (%)
STD group	
Yes	6 (14)
No	36 (86)
EEN group	
Yes	6 (11.1)
No	48 (88.9)

The differences between the two groups for the development of minor complications (nausea, vomiting, bowel function; diarrhoea and constipation) reduced prior to discharge, with no statistical differences between groups on discharge.

Comparison of Pain Scores

Pain scores were compared for the first seven post-operative days. The pain scores were ranked on a scale of 1-4. The scores were comparable for the first 5 post-operative days. On day 6, the difference in pain scores was approaching significance (Chi=10.9; p=0.07). The results are presented in table 3.34. The differences in pain scores for the two groups may have been attributed to quicker resumption of bowel function in the EEN group.

Table 3.34 Pain scores for the first seven days post-operatively

Post op Day	Standard Group N (%)	Enteral Group N (%)	Chi (p)
1			
no pain	8 (19)	17 (31)	5.74 (0.44)
mild	11 (26)	17 (31)	
moderate	18 (43)	12 (22)	
severe	5 (12)	8 (15)	
2			
no pain	2 (5)	3 (5.5)	3.75 (0.42)
mild	15 (36)	25 (46)	
moderate	12 (28)	17 (31.5)	
severe	13 (31)	9 (17)	
3			
no pain	6 (14)	12 (22)	9.74 (0.11)
mild	16 (38)	18 (33)	
moderate	13 (30)	9 (17)	
severe	7 (17)	15 (28)	
4			
no pain	13 (31)	25 (46)	5.63 (0.39)
mild	13 (31)	9 (17)	
moderate	11 (26)	14 (26)	
severe	5 (12)	6 (11)	
5			
no pain	9 (21)	27 (50)	10.9 (0.07)
mild	12 (29)	11 (20)	
moderate	15 (36)	8 (15)	
severe	6 (14)	8 (15)	
6			
no pain	8 (19)	23 (44)	9.91 (0.07)
mild	22 (52)	16 (30)	
moderate	8 (19)	10 (19)	
severe	4 (10)	4 (7)	
7			
no pain	19 (45)	32 (60)	6.48 (0.31)
mild	13 (31)	7 (13)	
moderate	8 (19)	11 (20)	
severe	2 (5)	2 (4)	

3.6.6 Post-operative Recovery of Mobility

The difference stages of mobilisation were compared for the first 12 post-operative days (table 3.35). There were no statistically significant differences between the two-randomised groups.

Exploration of the data demonstrated a small trend for the STD group to mobilise independently more quickly than the EEN group by day 7 post-operatively (11.9% (N=5) versus 5.5% (N=3)).

This may be attributed to the EEN group being connected to the feeding pump, as at day 12, 14.2% (N=6) of the STD group compared to 18.5% (N=10) of the enteral group were mobilizing independently.

Table 3.35 Number of Patients (%) achieving different stages of mobilization in the post-operative phase by randomised group

Stages of Mobilisation	Day 3 N (%)	Day 5 N (%)	Day 7 N (%)	Day 12 N (%)
Lying in bed				
Standard Group	29 (69)	7 (16.6)	5 (11.9)	1 (2.3)
Enteral Group	26 (48)	11 (20.3)	5 (9.2)	2 (3.7)
Sitting in Chair				
Standard Group	9 (21)	14 (47)	12 (28.5)	8 (19)
Enteral Group	22 (40)	15 (38)	8 (14.8)	6 (11.1)
Mobilising around bed				
Standard Group	3 (7)	4 (13)	3 (7.1)	7 (16.6)
Enteral Group	7 (13)	12 (3)	9 (16.6)	4 (7.4)
Mobilising with assistance				
Standard Group	1 (2)	2 (6)	7 (16.6)	5 (12)
Enteral Group	0 (0)	0 (0)	12 (34.5)	14 (25.9)
Mobilising independently				
Standard Group	0 (0)	2 (4.7)	5 (11.9)	6 (14.2)
Enteral Group	0 (0)	0 (0)	3 (5.5)	10 (18.5)

3.6.7 Post-operative Fluid balance

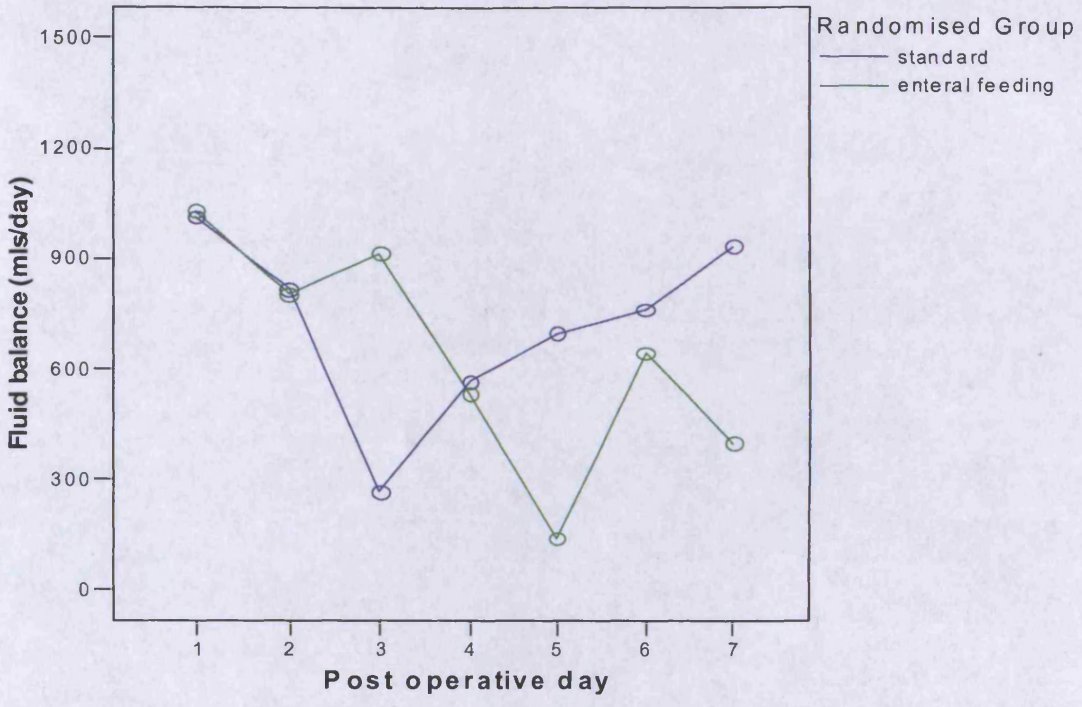
The mean fluid balance for the two randomised groups was compared post-operatively (table 3.36). The difference between the two groups for daily fluid balance reached significance over the first 7 post-operative days ($F_{1,70}$=766.8; p>0.0001).

The STD group was in a greater cumulative positive fluid balance for the first 7 days post-operatively (5123 mls) when compared to the EEN group (4053 mls). The mean difference was 1070 mls.

Table 3.36 Mean daily fluid balance (millilitres)

Fluid Balance	Standard Groups N=35 Mean (SD)	Enteral Group N=45 Mean (SD)	ANOVA
Day 1	1012 (1144)	1029 (1045)	($F_{1,78}$=148; p>0.0001)
Day 2	815 (1158)	801 (1049)	
Day 3	264 (851)	913 (1303)	
Day 4	564 (1269)	530 (1040)	
Day 5	695 (944)	139 (974)	
Day 7	761 (1338	641 (856)	
Day 12	934 (1053)	397 (655)	

Figure 3.5 Mean daily fluid balance (millilitres)



($F_{1,78}$=148; p>0.0001).

The use of Intravenous (IV) Fluids

The daily volume of intravenous fluids infused for the two-randomisation groups was collected daily for the first 7 days post-operatively (table 3.37).

The mean volume of IV fluids prescribed was significantly higher in the STD group for the first 7 days post-operatively when compared to the EEN group. The volume of IV fluids prescribed in the enteral nutrition decreased over the first 7 days post-operatively.

This is attributed to the use of EN to provide fluid requirements in the EEN group with subsequent reduction in the volume of intravenous fluid required.

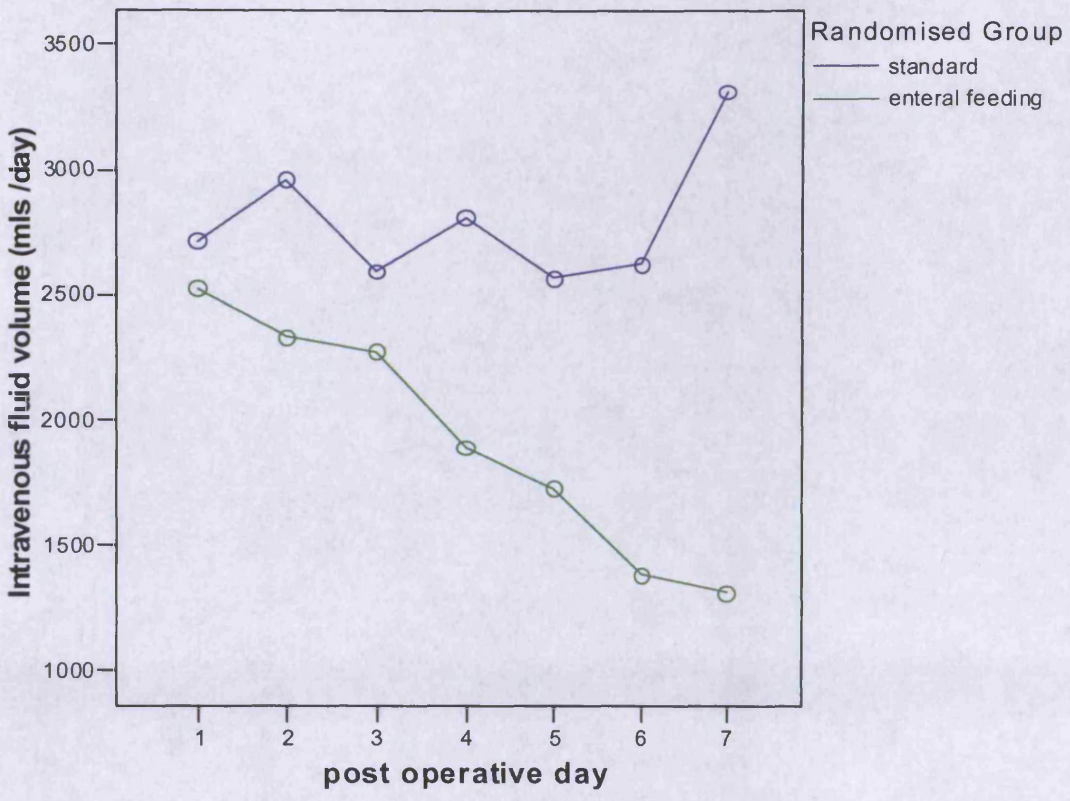
Table 3.37 Mean daily volume of intravenous fluids (millilitres) delivered a comparison of randomisation groups

Post operative day	Standard Group N=35 Mean IV fluid vol delivered/day mls (SD)	Enteral Group N=37 Mean IV fluid vol delivered/day mls (SD)
1	2713 (701)	2524 (911)
2	2960 (888)	2329 (762)
3	2593 (753)	2270 (1082)
4	2810 (868)	1889 (910)
5	2566 (937)	1726 (1150)
6	2620 (760)	1379 (1059)
7	3312 (4682)	1308 (1086)
Total cumulative intake	19574 mls	13425 mls

($F_{1,70}$=766.8; p>0.0001).

The volume of intravenous fluids delivered increased throughout the course of the first week and averaged between 2500-3000mls/day in the STD group. The mean volume then increased to a mean of 3000 mls/day on day 7 (figure 3.6)

Figure 3.6 Mean daily volume of intravenous fluids (millilitres) delivered



($F_{1,70}$=766.8; p>0.0001).

The development of Oedema

The development of oedema was compared for the first 7 days post-operatively (table 3.38). Fifteen patients (36.6%) of the standard group compared to four patients (8%) of the enteral nutrition group developed oedema (Chi square=12.0;p=0.0001).

Table 3.38 Number of patients and percentage who developed oedema in the 1st week post-operative

Oedema in 1 st week?	Standard Group N (%)	Enteral Group N (%)	Chi (p)
Yes	15 (36.6)	4 (7.5)	12.0 (0.0001)
No	26 (63.4)	48 (92.5)	
Total	41	52	

3.6.8 Nutritional Parameters

This section presents the results of the comparisons of the nutritional parameters post-operatively and post-discharge by randomised group.

Nutritional parameters have been used as surrogate outcome indicators in many clinical nutrition trials and are therefore important for use in the comparisons of efficacy of EN versus STD management. Results will be presented on the following:

1. Nitrogen balance
2. Weight
3. Mid upper muscle circumference
4. Handdynanometry
5. Oral intake and appetite
6. Biochemical parameters

Nitrogen Balance

A subgroup of patients in the total study population had a 24-hour urine collection for nitrogen balance performed. Many of the samples collected were not analysed as in many cases the timing on the collection was at the weekend, and only emergency samples were analysed. Results for the subgroup (N=44) are presented in table 3.39, by randomised group.

The difference between the groups was statistically significant; with the entire STD group in a negative nitrogen balance on day 5 post-operatively compared to

11 (47.8%) of the EEN group (Chi 22.2; p=0.01). Eight patients (34.7%) in the enteral nutrition group were in a positive nitrogen balance on day 5.

Table 3.39 Comparison of Nitrogen Balance on Day 5 Post-Operatively

Nitrogen balance	Standard Group N (%)	Enteral Group N (%)	Total N (%)
More than 10grams–ve	8 (38.1)	1 (4.5)	9 (21)
6-10 grams –ve	6 (28.5)	2 (8.6)	8 (18)
1-5.9grams –ve	7(33.4)	8 (34.7)	15 (34)
Equilibrium	0 (0)	4 (17.3)	4 (9)
1-6 gram +ve	0 (0)	7 (30.4)	7 (16)
More than 6gram +ve	0 (0)	1 (4.5)	1 (2)
Total	21 (100)	23 (100)	44 (100)

Weight

All patients in the study lost weight during their hospital stay (mean percentage weight loss of 4.2% from pre-operative day 1 to day of discharge). The results of the mean weight throughout the study are presented in table 3.40.

The mean weight on discharge of the STD group was 69.2 kg (SD 15.1 kg) and 72.2kg (SD 17.1kg) for the EEN group (NS). The mean drop in weight for the STD group was 4.6 kg (6.2% weight loss) and the mean drop for the EEN group was 2.1kg (3% weight loss). None of the mean weights were statistically significantly different.

Table 3.40 Comparison of Mean Weight (in Kilograms) by Randomisation Group

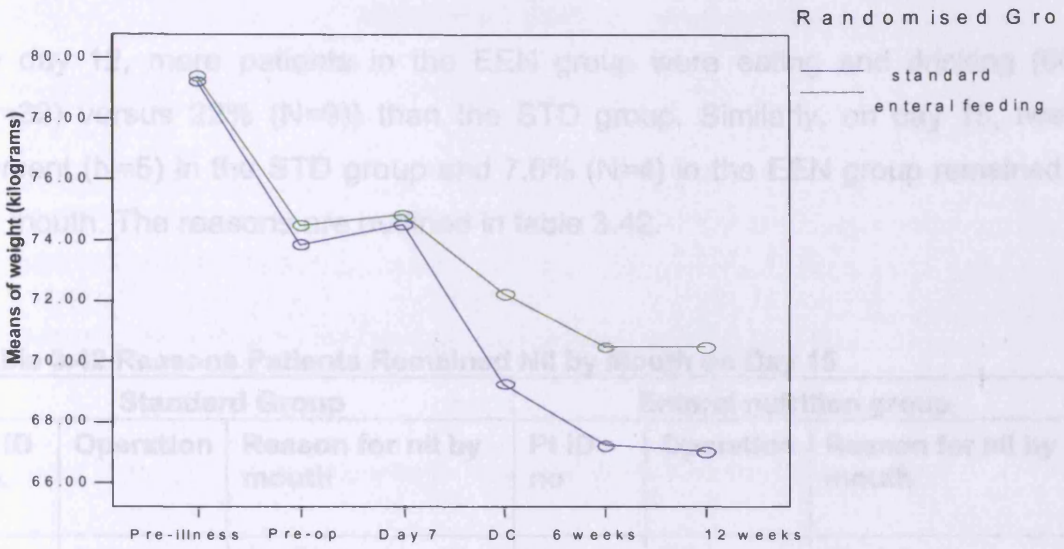
Weight (kilograms)	Standard Group Mean (SD)	Enteral Nutrition group	t-test (p)
Pre-illness	79.2 (14.9)	79.4 (16.4)	NS
Pre-operative	73.8 (16.0)	74.5 (17.5)	NS
Day 7	74.5 (14.4)	74.8 (18.1)	NS
Discharge	69.2 (15.1)	72.2 (17.1)	NS
6 weeks follow up	67.2 (14.3)	70.5 (16.9)	NS
12 weeks follow up	66.9 (13.9)	70.5(16.8)	NS

Table 3.41 shows the weight changes from pre-operatively to 6 weeks post-operatively were 6.6 kg (SD 4.4kg) for the STD group and 3.9 kg (SD 4.5kg) for the EEN group (t=2.96; p=0.004). It is clinically relevant that weight loss in the enteral nutrition group appears to be accelerated post-discharge (figure 3.7). The mean weight loss post discharge in the EEN group was 7.5 kg (SD 6.6kg) versus 2.0kg (SD 2.7Kg) in the STD group. This reached statistical significance (t=-2.09; p<0.05).

Table 3.41 Mean Changes in Weight (in Kilograms) over the study period and follow-up (kilograms)

Changes in weight	Standard Group Weight change Kg (SD)	Enteral Group Weight change Kg (SD)	t-test (p)
Pre-op to 7 days post-op	-0.65 (4.9)	-0.22 (2.2)	NS
Pre-op to discharge	4.6 (3.5)	2.1 (3.2)	3.5, df 94 (0.001)
Pre-op to 6 weeks	6.6 (4.4)	3.9 (4.5)	2.96 df 94 (0.004)
Pre-op to 12 weeks	1.7 (6.3)	3.8 (4.6)	2.89 df 94 (0.005)
Discharge to 6 weeks	2.0 (2.7)	1.7 (6.6)	-2.09 df 94 (p<0.05)
Discharge to 12 weeks	2.2 (2.6)	1.8 (3.3)	NS
6 weeks to 12 weeks	0.2 (2.6)	-0.04 (1.6)	NS

Figure 3.7 Mean changes in weight (kg) of the Randomised Groups over the duration of the study



$F_{1,89}$ =1919; p<0.0001

Oral food intake

Resumption of oral drinks and food post-operatively is a key stage used to indicate 'recovery' in surgical practice. Fluids and foods are usually reintroduced on day 4-5 post-operatively for gastrectomy patients, day 7-8 for oesophagectomy and pancreatic resection. Patients typically undergo a contrast swallow prior to commencing oral fluids and diet to ensure the UGI anastomoses are intact.

Oral diet was commenced on the fifth post-operative day in one patient undergoing partial gastrectomy in the STD group and two patients undergoing sub-total gastrectomy in the EEN group.

By day 7 post-operatively, eight of the STD group (18.6%) and 9 patients (16.6%) of the EEN group were commenced on oral diet. By day nine, 36%

(N=15) of the STD group had commenced oral diet and 44% (N=24) of the EEN group had commenced oral diet.

By day 12, more patients in the EEN group were eating and drinking (60% (N=32) versus 22% (N=9)) than the STD group. Similarly, on day 15, twelve percent (N=5) in the STD group and 7.6% (N=4) in the EEN group remained nil by mouth. The reasons are outlined in table 3.42.

Table 3.42 Reasons Patients Remained Nil by Mouth on Day 15

Standard Group			Enteral nutrition group		
Pt ID no.	**Operation**	**Reason for nil by mouth**	**Pt ID no**	**Operation**	**Reason for nil by mouth**
13	IL	Respiratory problems	67	GS	Chylothorax
14	IL	Leak	89	GS	Leak
17	PG	Leak	90	PPPD	Delayed gastric emptying
28	PPPD	Leak	91	PPPD	Chest infection
40	PPPD	Leak			

Leak = anastomotic leak, IL= Ivor Lewis oesophagectomy, PG=partial gastrectomy; PPPD= pylorus preserving pancreaticoduodenectomy; GS= gastrectomy

The mean calorie intakes were compared over time. The EEN group consistently had a higher mean calorie intake as compared to the STD group.

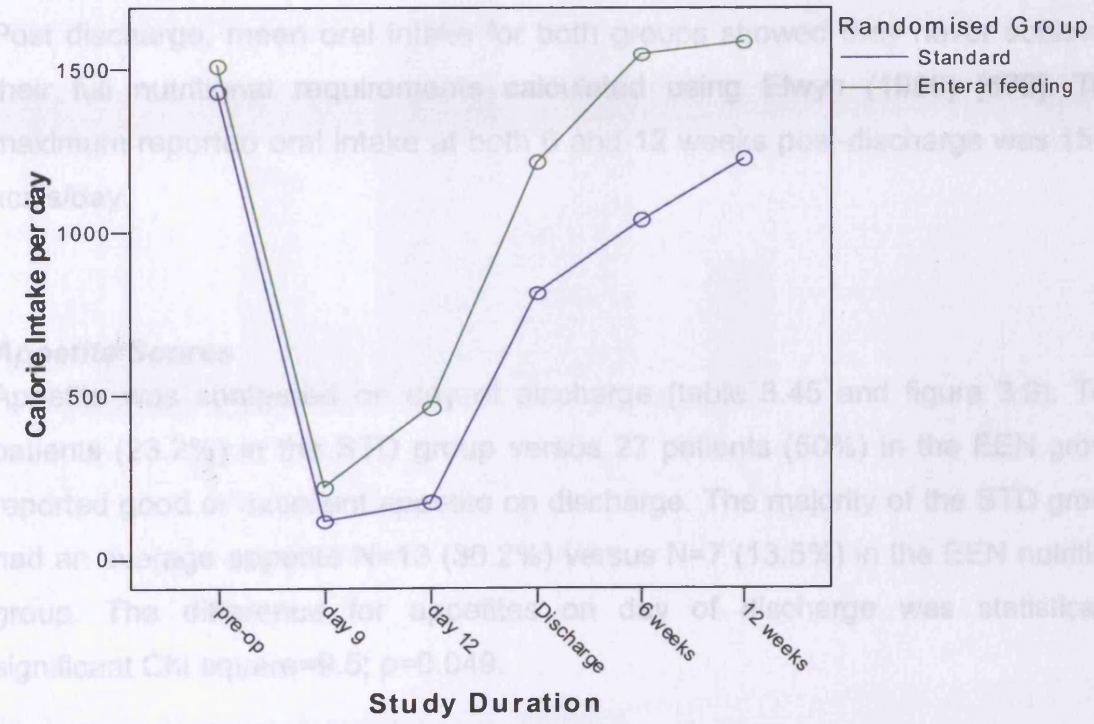
The difference between the groups for mean oral calorie intakes over time was statistically significant ($F_{1,\ 86}$=1682.6;p<0.0001). The results are presented in table 3.43 below and illustrated in figure 3.8.

Table 3.43 Mean oral calorie intake by Randomisation Group over time

Oral calorie intake	Standard Group N=38 Mean intake calorie/day (SD)	Enteral Group N=50 Mean intake calories/day (SD)	ANOVA (p)
Pre-operative	1429 (415)	1508 (457)	$F_{1,86}$=1682.6; p<0.0001
Day 9 post op	113 (203)	218 (203)	
Day 12 post op	172 (231)	466 (418)	
Day of discharge	812 (242)	1227 (421)	
6 weeks post discharge	1036 (334)	1544 (444)	
12 weeks post discharge	1225 (376)	1582 (443)	

Missing data= 4 in standard group; 4 in enteral nutrition group

Figure 3.8 Mean oral calorie intake by Randomisation Group over time



$F_{1,86}$=1682.6;p<0.0001

Oral calorie intakes were categorized and analysed on discharge and at follow up. Eighty-three percent (N=35) of the STD group achieved a mean calorie intake less than 1000kcals/day at discharge. In comparison 30% (N=16) of patients in the EEN group were having a mean calorie intake less than 1000 kcals/day (Chi squared =32.14; $p<0.0001$).

Table 3.44 Oral intake (calories/day) on day of discharge by randomised group

Oral intake on day of discharge	Standard Group N (%)	Enteral Group N (%)	Total Study Population
> 600 calories	4 (10)	2 (4)	6 (6)
700-1000 calories	30 (73)	11 (21)	41 (45)
1000-1500 calories	7 (17)	31 (61)	38 (41)
1600-2000 calories	0 (0)	7 (14)	7 (8)
Total	41 (100)	51 (100)	92 (100)

Missing data = 1 in standard group and 3 in enteral nutrition group

Post discharge, mean oral intake for both groups showed they never achieved their full nutritional requirements calculated using Elwyn (1980) [572]. The maximum reported oral intake at both 6 and 12 weeks post-discharge was 1500 kcals/day.

Appetite Scores

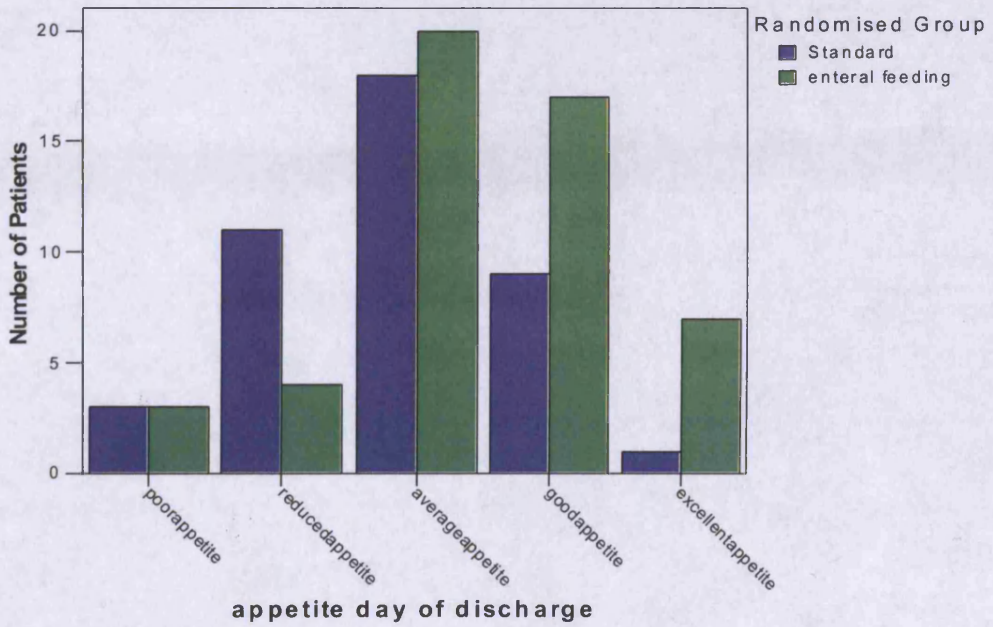
Appetite was compared on day of discharge (table 3.45 and figure 3.9). Ten patients (23.2%) in the STD group versus 27 patients (50%) in the EEN group reported good or excellent appetite on discharge. The majority of the STD group had an average appetite N=13 (30.2%) versus N=7 (13.5%) in the EEN nutrition group. The difference for appetites on day of discharge was statistically significant Chi square=9.5; p=0.049.

Table 3.45 Reported Appetites on Day of Discharge by Randomised Group

Appetite reported on day of discharge	Standard Group N (%)	Enteral Group N (%)	Total Study Population N (%)
Poor Appetite	3 (7.1)	3 (5.6)	6 (6.3)
Reduced Appetite	11 (26.3)	4 (7.4)	15 (15.8)
Average appetite	18 (43.3)	20 (37)	38 (39.5)
Good appetite	9 (21)	17 (31.5)	26 (27)
Excellent Appetite	1(2.3)	10 (18.5)	11 (11.4)
Total	42 (100)	54 (100)	96 (100)

Chi =9.5; df 8 p=0.049

Figure 3.9 Comparison of appetite on day of discharge



Mid Upper Muscle Circumference (MUMC)

Mid upper muscle circumference was compared peri-operatively. No significant differences occurred in mean MUMC over time. The results are presented in table 3.46.

Table 3.46 Mid Upper Muscle Circumference (mms) Peri-operatively

	Standard group N=34 Mean (SD)	Enteral Group N=48 Mean (SD)	Total group N=82 Mean (SD)
Pre-op	30.7 (4.9)	28.8 (7.2)	29.6 (6.4)
Discharge	26.3 (4.4)	25.3 (6.3)	25.8 (5.6)
6 weeks post-op	23.6 (3.5)	24.7 (5.4)	24.3 (4.7)
12 weeks post-op	22.8 (3.5)	24.4 (5.2)	23.7 (4.6)

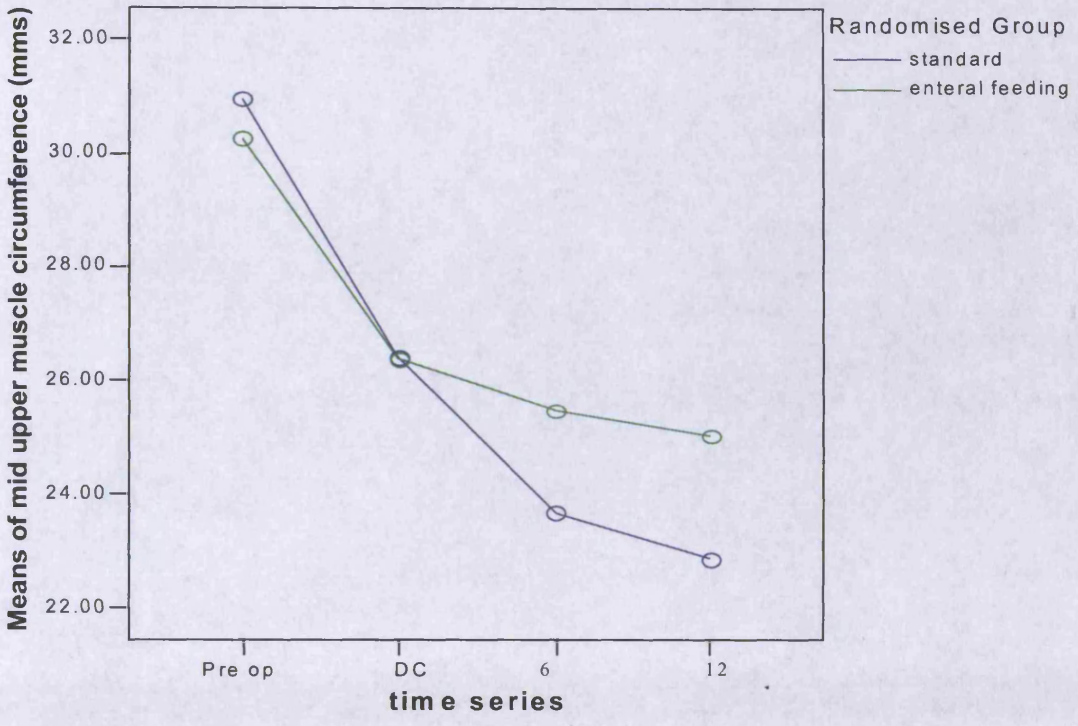
The mean changes in MUMC are presented in table 3.46 below. The STD group had more pronounced muscle loss than the EEN group on discharge, 6 weeks and 12 weeks post-discharge. Loss of muscle mass appeared to plateau at 6 weeks whereas in the STD group muscle mass continued to decrease (figure 3.10).

Table 3.47 Mean changes in Mid Upper Muscle Circumference Peri-operatively

	STD Group Mean changes MUMC in mm (SD) N=34	EEN Group Mean changes MUMC (mm) (SD) N=49	T test (p)
Pre-op to DC	-4.4 (2.9)	-3.5 (2.5)	NS
Pre-op to 6 weeks	-7.0 (5.3)	-4.1 (4.2)	-4.56 (<0.0001)
Pre-op to 12 weeks	-7.9 (6.6)	-4.4 (5.5)	-1.53 (<0.0001)

(DC= discharge; Pre-op= pre-operative)

Figure 3.10 Mid Upper Muscle Circumference (mms) peri-operatively and at follow up



$F_{1,69}$=2073; p<0.0001

Handdynanometry (HD)

All patients in the study had a reduction in HD and suggesting a reduction in muscle strength. The reduction in HD from pre-operative stage to discharge was statistically significant between the two groups (t=2.96;p=0.004). The EEN group had less reduction in hand-grip strength than the standard group (2.7 mmHg versus 5.72 mmHg).

Table 3.48 Mean changes in Handdynanometry (mmHg) readings from pre-operative period to discharge

Handdynanometry measurement	Standard Group mean (SD)	Enteral Group mean (SD)	t-test (p)
Pre-operative HD (mmHg)	34 (10.8)	30.7 (10.8)	NS
Discharge HD (mmHg)	28.2 (9.7)	29 (9.2)	NS
Difference from pre-op to discharge (mmHg)	5.72 (1.1)	2.7 (1.6)	2.96; (p=0.004)

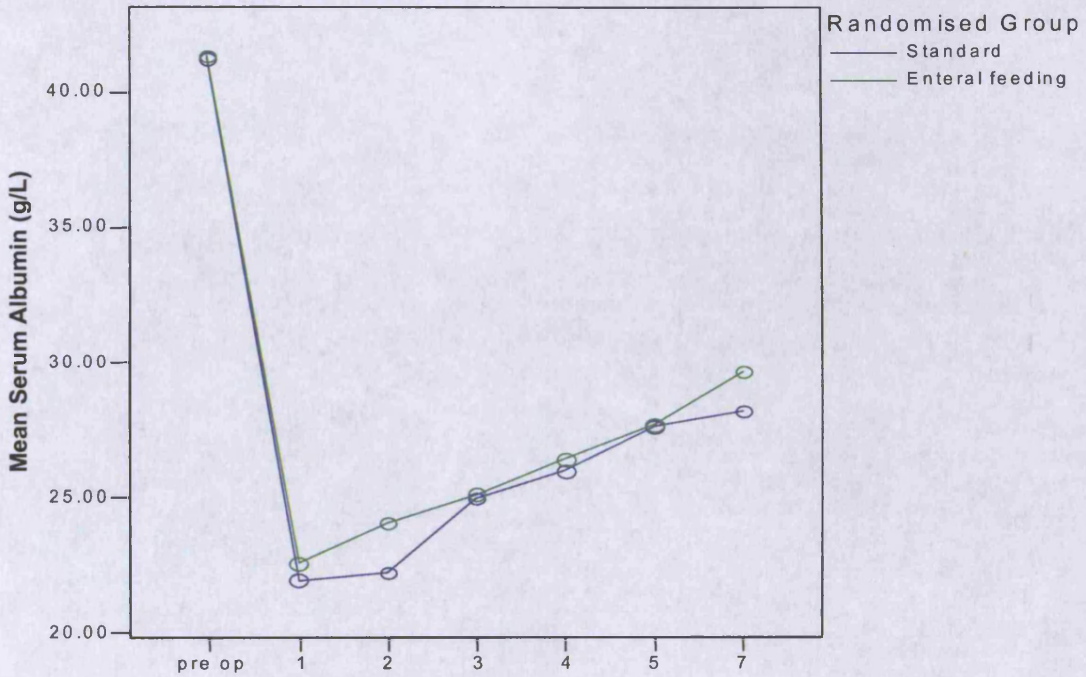
3.6.9 Biochemical Parameters

Serum Albumin

Serum albumin was assayed daily over the first 7 days post-operatively. As part of the normal care pathway, all patients post major UGIT surgery should have had daily albumin levels. In this RCT, twenty-four patients did not have daily bloods tests taken during this period. These patients were from both randomised groups.

There were no statistically significant between the two groups for the first seven days post-operatively. All patients in the total study population had a drop in serum albumin of 8-9g on Day 1 post-operatively. The mean serum level then gradually increased over the next 7 days (figure 3.11).

Figure 3.11 Serum albumin concentration in the first seven days post-operatively



$F_{1,70}$=1628;p=0.543

Eighty two percent (N=79) of the study population successfully had serum albumin collected on discharge.

Fifty patients (79%) in the STD and EEN group had a serum albumin greater than 30g/l on the day of discharge. The mean albumin level on discharge was 32.2g/l (SD 5.2) for the STD group and 33.9g/l (SD 4.2) for the EEN group. Both levels were within the normal range. There were no significant differences in serum albumin on day of discharge (t=-1.70; p=0.092). The results are presented in table 3.49.

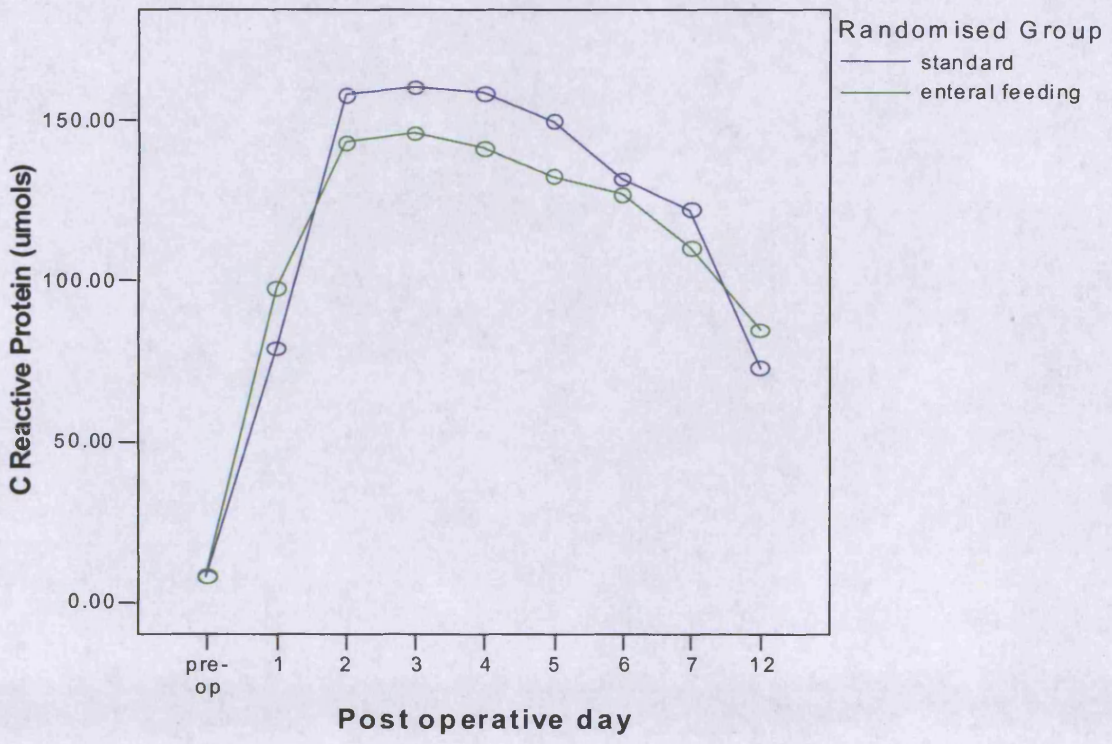
Table 3.49 Serum albumin concentration on day of discharge

Albumin level mmol/litre	Standard group N=41 N (%)	Enteral group N=53 N (%)	Total study N=94 N (%)
19-25	5 (12)	1 (1.8)	6 (6.4)
26-30	6 (14.6)	7 (13.2)	13 (13.8)
31-35	18 (44.4)	19 (36)	37 (39.4)
Greater than 36	12 (29)	26 (49)	38 (40.4)

C-Reactive Protein (CRP)

Sixty eight percent of the study population had CRP collected daily for the first 7 days post-operatively. There were no differences between the two groups postoperatively for the first 7 days. The data from the total study population illustrates that CRP is synthesised during the 24-48 hours post-operatively, peaking on day 3 post-operatively (figure 3.12). There were no statistically significant differences between the two groups for CRP over the first 7 days post-operatively.

Figure 3.12 Mean C-reactive protein (umols) for the first seven days post-operatively



3.6.10 Summary of Discharge Parameters

A summary of both the continuous and categorical data recorded on the day of discharge are presented in the table 3.50. There were no significant differences between the two groups in terms of weight, appetite score, handdynanometry, mid upper arm circumference, albumin, bowel function, and nausea.

The difference on discharge for the presence of oedema was statistically different. More patients in the STD group were discharged with oedema when compared to the EEN group. (Seven patients (37.7%) in the STD group compared to 2 patients (16.6%) in the EEN group (chi=4.54; p=0.033).

There were no significant differences between the groups with regards to use of analgesia or ability to mobilise on discharge.

The majority of patients (92.5%) in the EEN group were able to mobilise independently on discharge. More patients in the STD group (16.7%) as compared to the EEN group (5.4%) were dependent on assistance to mobilise on discharge.

Table 3.50 Summary of Nutritional Parameters on the Day of Discharge

Nutritional Parameters	**Standard Group Mean (SD)**	**Enteral Nutrition Mean (SD)**	**Statistical test (p)**
Weight (kilograms) Mean (SD)	69.2 (15)	71.5 (16)	NS
Oral Intake (calories) Mean (SD)	830 (257)	1224 (445)	t=4.99 (>0.0001)
Handdynanometry Mean (SD)	28.4 (9.8)	28.0 (9.2)	NS
Mid Upper Muscle Group Mean (SD)	26.3 (4.3)	25.3 (6.2)	NS
Appetite mean scores Mean (SD)	2.86 (0.9)	3.4 (1.0)	NS
Nausea day of Discharge N (%)	3 (7.1)	1 (1.9)	NS
Bowel Function day of discharge Constipation Normal stool Loose Stools Diarrhoea N (%)	 2 (4.7) 35(83.3) 0(0) 5(11.9)	 5(9.3) 42 (77.7) 1(2) 6 (11)	NS
Oedema present day of Discharge N (%)	7 (16.6)	2 (37.7)	Chi = 4.54(0.033)
Analgesia Requirements N (%) No analgesia Paracetamol only Tramadol Missing data	 1 (2.4) 24 (57) 7 (23.8) 10 (23.8)	 0 (0) 19 (35.3) 15 (27.7) 20 (37)	NS
Mobilisation day of Discharge N (%) Lying in bed Mobilising around bed Mobilising with assistance Mobilising no assistance	 1 (2.4) 2 (4.8) 7 (16.7) 31 (73.8)	 0 (0) 1 (1.9) 3 (5.6) 50 (92.5)	NS

3.6.11 Estimation of Cost Differences

This section will present the results of the cost difference between the two randomised groups for the MCRCT. The aim is to provide an estimate of the differing costs associated with each group.

There were several assumptions for the calculation of costs for the two groups. These are listed below:

1) This cost estimation was based on the knowledge that the groups had similar costs for the delivery of the routine care pathway, for patients undergoing major UGI resection. Thus routine health expenditure was deemed similar for both groups.

2) The differential costs per group were used to determine the cost difference for the purpose of this RCT.

3) The differential costs were taken as the difference in LOHS and the costs of treating the significantly different major complications. These were considered to be the main cost drivers. The cost of LOHS has been used to calculate cost differences in other studies [12, 530].

4) All costs of equipment were calculated from manufacturers' list prices.

5) The cost of drugs, dressings and enteral nutrition is based on the British National Formulary (BNF)[614].

6) The grades of medical and health professionals were taken as mean of pay scale, using current pay scales, based on Agenda for Change, Department of Health (UK) [615].

7) The jejunostomy tube is inserted as an adjunct to the operative procedure theatre time and was therefore not included in the costs. Only consultant and nurse time was calculated.

8) The cost of the feeding pumps was not included. These are supplied from the enteral nutrition companies as part of the Local Contractual agreement and are usually provided free of charge within the enteral feed contract.

Cost of providing intervention

The cost of delivering enteral nutrition per patient was £270.11 per patient for 7 days (table 3.51).

Justification of Costs

1) Consultant time.

The Consultant Surgeons each performed the insertion of the jejunostomy tube for the MCRCT. Each consultant was asked to record the time taken to insert the jejunostomy at the end of the main surgical procedure. The insertion time averaged 20 minutes for the four surgeons. The cost per hour of a Consultant Surgeon is £47.40 [615]. In addition, the cost of a theatre nurse was also calculated based on mean scale band 6 nurse for 20 minutes. The combined cost of insertion of the jejunostomy was calculated to be £60.

2) Cost of jejunostomy tube.

The jejunostomy tube used was the Fresenius *Freka* ® (Liverpool, UK) needle catheter jejunostomy. The cost per unit as reported by the manufacturer was £90.

3) Cost of dressing

The dressing used for the jejunostomy tube for patients in the study was Lyofoam® (7.5cm X7.5 cm). The BNF [614] price is 97p per unit. The dressing was changed every day.

4) Cost of giving sets

A giving set connects the needle catheter jejunostomy to the feed reservoir. In line with MHRA [616] recommendations, one giving set can be used for each patient for delivering sterile feeds per 24 hours. The unit price as per manufacturer was £3.76 per unit.

5) Cost of feeding pump

The cost of the feeding pump to administer the enteral feed was not included in the cost of administering the enteral nutrition. Most commercial enteral nutrition companies supply pumps as part of the local contractual agreement.

6) Nursing time

The nursing time taken to set up the administration of the enteral feeding (flush the jejunostomy with sterile water, connect the enteral feeding) and check the percutaneous entry site (for leakage, complications and sign of infection) was estimated to be 20 minutes per day. The grade of nursing staff was taken as mid scale Band 5 (agenda for change) [615]. This equates to £28,000 gross costs per annum [615]. The hourly rate was £15 per hour. Thus for 20 minutes of nursing time, the cost is taken as £5.

7) Dietetic time

The dietetic time needed to determine nutritional requirements, monitor tolerance of enteral feed and calculate enteral nutrition regimen was estimated to be 30 minutes per patient per day. The grade of dietitian was taken as Band 7 top of scale [615]. This was taken as £45,000 per annum gross cost. This equates to £23.07 per hour.

8) Length of time of Intervention

The length of time of the intervention was taken to be 7 days. Therefore the cost of delivering enteral nutrition to a patient in the enteral nutrition group was taken as £270.11.

9) Cost of Inpatient Stay

The cost per day for inpatient stay was based on figures from the Welsh Assembly Government [617] . The cost is £220 per patient per day. This is the cost of a general ward hospital bed only and does not include cost of diagnosing or treating the development of any minor or major complications.

Table 3.51 The Calculation of Cost of Delivering Enteral Feed per Day to Study Patients

Cost	Justification of cost	Price
Insertion of jejunostomy tube	20 minutes of Consultant time 20 minutes theatre nurse time (Top of Band 6)	£20 £10
Cost of jejunostomy tube	*Fresenius* list price [618]	£90
Cost of jejunostomy insertion		£120
Costs of dressing	BNF price [615]	0.97 per unit
Costs of Giving set/day (single use)	*Abbott Laboratories* list price [619]	£3.76 per unit
Feed pumps	Not included	£0
Nursing time	Top of scale Band 5	£5.00 for 20 minutes
Dietetic time	Top of scale Band 7	£11.00 for 20 minutes
Cost of enteral feed per day	BNF price [615] for Osmolite® (*Abbott laboratories*)	£5.00
Total		£25.73 day Total for 7 days= £180.11 + tube insertion= £270.11

Cost Estimation Calculation

The cost of LOHS was calculated using the median and interquartile range for LOHS determined from the results of this RCT. The calculation of the cost difference in LOHS for the groups is presented in table 3.52.

The cost for the LOHS for a patient in the enteral nutrition group was £3520 (IQ range £2860-£4840). When the cost of delivering enteral nutrition for the 7 day intervention period is added, the total cost attributed to the median LOHS is £3790.11(£3130.11-5110.11).

In comparison the cost of LOHS for a patient in the standard group was £4400 (IQ range £3245-£6160). Interventional costs for the standard group were not included, despite the cost of the increased intravenous fluids prescribed and administered. These costs were considered minimal. The cost of delivering the enteral feed to the patients (n=6) who received enteral nutrition in the standard group was also not included in the cost estimation.

Therefore, the cost difference for treating the differing LOHS for the two groups was £609.89 (114.89-1049.80) per patient when enteral nutrition used.

Table 3.52 Estimation of Cost for Length of Hospital stays for Both Randomisation Groups

Enteral Group

LOHS for the Enteral nutrition group median =16 days (Inter Quartile (IQ) range 13-22 days)
Cost of LOHS for the enteral nutrition group was £3520 (IQ range £2860-£4840 per patient
+ Cost of Intervention =£270.11 per patient
Total Cost of LOHS=£3790.11 (IQ range = £3130.11-£5110.11)

Standard Group

LOHS for the Standard group was 20 days (IQ range 14.75-28 days)
Cost of LOHS for the standard group was £4400 (IQ range £3245-£6160) per patient
+ cost of intervention=£0 per patient
Total cost of LOHS= £4400 (IQ range £3245-£6160)

Cost Difference between two groups

Cost Saving of £609.80 (IQ range £114.80-£1049.89) per patient when enteral nutrition used

Cost of Treating the Major Complications

The costs of treating the statistically significant different major complications were calculated. All other costs attributed to the development of non-significant complications were assumed to be similar for the two randomised groups. The costs are outlined in table 3.53. A more detailed table outlining the calculation of cost for each complication and a justification of these costs are presented in table III.III.I-III.III.III in appendix III.

Table 3.53 Summary of the Costs of the Major Complications used in the cost estimation

Major Complication	Cost per day
Chest Infection*	£147
Wound Infection*	£107
Anastomotic leak*	£135-1157 per day

* Statistically significant complications, The cost of returning to theatre and radiology costs are not included in the cost of anastomotic leak.

The total costs of treating the significantly different complications in the standard group were £29,965.80-£179,151.24. This equates to £713.47-£4,265.51 per patient in the standard group. The major contributor to this cost is the expenditure associated with treating the seven patients who developed anastomotic leaks. These patients remained in hospital for a total of 142 additional days as a result of this major complication. This averaged 3.4 days for every patient in the standard group (N=42). The patients may require a period of time on critical care for ventilatory support and may require a return to the operating theatre for further explorative surgery. Thus calculation and estimation of these costs is difficult. The treatment of anastomotic leaks varies in clinical practice. This is the reason for the variation in the costs calculation. All patients in this RCT returned to critical care after developing an anastomotic leak.

The cost of treating major complications in the enteral nutrition group was £4,480-£13,680. This equates to £82.30 to £253.33 per patient in the enteral

nutrition group. Once again the variation in costs is attributed to the cost of treating the one patient who developed an anastomotic leak in the enteral nutrition group.

The cost difference of treating the major complications between the group was £631.17 to £4,012.18, if enteral nutrition was used. The calculations for the cost differences for the differences in major complications are presented in table 3.54.

Table 3.54 Calculation of costs for the differences in major complications

Type of Complication	Standard Group N=42 Cost of Treating Complications per day				Enteral Nutrition Group N=54 Cost of Treating Complications per day			
	% (N)	Total no. of days with complication	No. of days per patient in group	Cost of treating Complications	% (N)	N of days for group with complication	No of days per patient in group	Cost of treating Complications
Wound Infection	28.5	95	2.26	£7125-£10165 [1]	3.7 (3)	7	0.13	£525-£749 [1]
Chest Infection	(12)	33	0.78	£3670.80-4692.24 [2]	9.3 (5)	25	0.46	£2875-£3675 [2]
Anastomotic Leak	21.4 (9)	142	3.4	£19170-£164294 [3]	2.2 (1)	8	0.15	£1080- 9256 [3]
	16.6 (7)							
Total cost	£29965.80-£179151.24				£4480-£13,680			
Cost per patients	£713.47-£4265.51				£82.30-£253.33			
Cost saving per patient with enteral nutrition	**£631.17-£4,012.18**							

[1] Cost of Wound Infection=£75-£107 per patient per day; [2] Cost of chest infection = £115-£147 per patient per day;. [3] Cost of treating anastomotic leak= £135-£1157 per patient per day.

The total cost estimation (based on LOHS and the statistically significant different major complications) is outlined in table 3.55. The total cost of the enteral nutrition group was £3709.52 (£3049.52 to £5864.96) per patient. The cost associated with the standard group was £5060.48 (£3905.48 to 10631.11) per patient.

The cost difference is £1350.96 (£855.96-£4766.15) per patient. This equates to the cost saving of using enteral nutrition post-operatively. The calculation for the cost analysis is presented in table 3.55.

Table 3.55 Cost Analysis Calculation

Cost per patient of treating major complications per patient £713.47-£4,265.51 in the standard group
Cost of LOHS=£4,400 (IQ range £3,245-£6,160)
Total cost for standard group per patient= £5,113.47 (£3,958.47-10,425.51)
Cost per patient of treating major complications =£82.30-£253.33 per enteral nutrition patient
Cost of LOHS per patient = £3520 (IQ range £2,860-£4,840) + Cost of providing enteral nutrition for intervention period=£270.11
Total costs for enteral nutrition group per patient=£3,872.41 (£3,130.11-£5,110.11)
COST SAVING FROM USING ENTERAL GROUP= £1241.06 (£828.36-£5,315.40 PER PATIENT

Summary of Cost Differences

This section has presented an estimate of the potential cost savings that can be made with the incorporation of early enteral nutrition into a patient care pathway.

Several assumptions have been made when calculating this cost estimate and it is important that reference again is made that this is not a health economic assessment of total cost expenditure. The summary of the cost analysis is presented in table 3.56.

Table 3.56 Cost Analysis Summary for Patients in Clinical Trial

	Standard Group N=42	**Enteral Group N=54**
Cost of intervention per patient for 7 days	£0*	£270.11per patient
Cost of LOHS	£4,400 (IQ range £3,245-£6,160)	£3,520 (IQ range £2,860-£4,840)
Cost of treating significantly different major complications	£713.47-£4,265.51	£82.30-£253.33
Total per patient	£5,113.47(£3,958.47-10,425.51)	£3,602.30 (£2,942.30-£5,093.33)
Cost Saving if enteral nutrition used per patient	**£1421.17 (£926.17-£5,242.18)**	

3.6.12 Results of Health Related Quality of Life

This section will present the results of the Health Related Quality of Life (HRQoL) questionnaires. HRQoL is an important outcome indicator. A comparison of HRQoL provides evidence of any potential benefit of the intervention in a holistic approach, and ensures any differences in clinical and financial outcomes do not convey deleterious consequences to the patient.

Response Rate

The SF-36 health related quality of life questionnaire was given to all patients pre-operatively, on discharge, at follow up at 6 weeks, 12 weeks, 6 months and 12 months. As the trial was still recruiting, not all patients have reached the key time points. The response rate for the return of questionnaires is presented in table 3.57. The reasons why patients did not respond were not recorded, as it was deemed inappropriate to question the patients.

Table 3.57 Response Rates for Completion of Health Related Quality of Life

Administration of SF-36 HRQoL Questionnaire	Response N
Baseline (pre-operative)	81
Discharge	78
6 weeks	78
12 weeks	78
12 months	58

Results of Health Related Quality of Life

This thesis will only present the data relating to HRQoL until 12 weeks post-operatively. This is because full data sets were not available or transformed at the time of this analysis.

The data was transformed as per SF-36 manual instructions [593]. Data will be presented for changes in HRQoL using the mean values obtained for either group. In addition, a comparison between the groups will subsequently be presented.

Baseline Comparison between the groups

The groups were compared at baseline (i.e. pre-operatively) for responses of HRQoL. The results are presented in table 3.58.

The groups were comparable for seven of the eight HRQoL factors pre-operatively. The scores for social functioning were however statistically different. The mean score was higher in the enteral nutrition group as compared to the standard group (t=-2.15; p=0.035).

Table 3.58 Comparison of Health Related Quality of Life scores at Baseline

HRQoL factor	Enteral Group Mean (SD)	Standard group Mean (SD)	T test (p)
General Health Status	55.8 (21.0)	59.4 (19.9)	0.76 (0.45)
Physical Function	58.5 (27.9)	67.2 (28.6)	1.41 (0.16)
Vitality	56.7 (29.4)	50.4 (28.1)	-0.97 (0.33)
Physical Role	29.3 (43.3)	25.0 (41.2)	-0.45 (0.65)
Bodily pain	68.8 (23.6)	59.1 (31.2)	-1.62 (0.10)
Mental score	68.7 (22.00	69.4 (21.8)	0.13 (0.9)
Emotional score	47.3 (48.4)	47.5 (44.4)	0.02 (0.9)
Social Functioning	63.3 (29.4)	48.3 (34.4)	-2.15 (0.035)*

*statistically different

The changes in HRQoL data for the 8 factors by randomisation group are presented in table 3.59. The results are illustrated in Figures III.III.I to III.III.VIII in Appendix III.

Table 3.59 Changes in Health Related Quality of Life Scores

HRQoL factor	Enteral Group Mean score (SD)	Standard group Mean score (SD)	T test (p)
General Health Status			
Score pre-op	55.8 (21.0)	59.4 (19.9)	0.76 (0.45)
Score on discharge	50.3 (20.3)	47.9 (19.9)	-0.53 (0.59)
Score at 6 weeks	47.8 (19.0)	49.9 (17.9)	0.49 (0.623)
Score at 12 weeks	51.3 (10.8)	49.9 (23.7)	-0.26 (0.79)
Difference pre-op to DC	-5.5 (22.7)	-11.5 (21.8)	-1.16 (0.25)
Difference DC to 6 weeks	-2.5 (18.4)	+2.0 (15.2)	1.18 (0.24)
Difference 6 weeks to 12 weeks	+ 3.5 (14.9)	+0.02 (23.2)	-0.76 (0.45)
Physical Function			
Score pre-op	58.5 (27.9)	67.2 (28.6)	1.41 (0.16)
Score on discharge	33.4 (22.9)	35.7 (20.6)	0.48 (0.63)
Score at 6 weeks	46.2 (24.3)	44.3 (22.5)	-0.35 (0.73)
Score at 12 weeks	52.9 (23.1)	49.3 (29.1)	-0.59 (0.55)
Difference pre-op to DC	-25.1 (28.9)	-31.5 (28.7)	-1.45 (0.15)
Difference DC to 6 weeks	+12.8 (23.7)	+8.6 (20.8)	-0.84 (0.40)
Difference 6 weeks to 12 weeks	+6.7 (20.3)	+5.0 (24.7)	0.45 (0.66)
Vitality			
Score pre-op	56.7 (29.4)	50.4 (28.1)	-0.97 (0.33)
Score on discharge	32.4 (24.4)	25.1 (14.2)	0.16 (0.11)
Score at 6 weeks	37.8 (20.9)	36.2 (19.9)	-0.36 (0.72)
Score at 12 weeks	47.7 (21.8)	44.4 (24.5)	-0.63 (0.53)
Difference pre-op to DC	-24.3 (28.5)	-25.3 (28.1)	-0.2 (0.84)
Difference DC to 6 weeks	+ 5.4 (23.9)	+11.1 (20.0)	1.11 (0.27)
Difference 6 weeks to 12 weeks	+ 9.9 (20.4)	+8.2 (18.0)	-0.47 (0.64)
Physical Role			
Score pre-op	29.3 (43.3)	25.0 (41.2)	-0.45 (0.65)
Score on discharge	4.4 (17.9)	0.69 (4.2)	-1.21 (0.23)
Score at 6 weeks	22.0 (40.2)	19.1 (41.7)	0.29 (0.77)
Score at 12 weeks	17.6 (35.6)	10 (24.3)	-1.0 (0.29)
Difference pre-op to DC	-24.9 (42.9)	-24.3 (39.1)	0.84 (0.41)
Difference DC to 6 weeks	+17.6 (49.5)	+18.4 (47.5)	-0.98 (0.33)
Difference 6 weeks to 12 weeks	-4.4 (46.6)	-9.1 (46.5)	0.22 (0.83)

*Statistically significant difference; DC= discharge

Table 3.59 Changes in Health Related Quality of Life Scores (continued)

HRQoL factor	Enteral Group Mean score (SD)	Standard group Mean score (SD)	T test (p)
Bodily pain			
Score pre-op	68.8 (23.6)	59.1 (31.2)	-1.62 (0.10)
Score on discharge	44.0 (27.3)	37.4 (23.6)	-1.13 (0.26)
Score at 6 weeks	57.4 (28.2)	44.7 (22.9)	-2.17 (0.03)*
Score at 12 weeks	63.6 (26.8)	48.4 (29.6)	-2.30 (0.02)*
Difference pre-op to DC	-24.8 (34.6)	-22.1 (32.3)	0.81 (0.42)
Difference DC to 6 weeks	+13.4 (26.6)	+7.3 (19.8)	-1.10 (0.25)
Difference 6 weeks to 12 weeks	+6.2 (23.3)	+3.7 (21.1)	-1.00 (0.28)
Mental score			
Score pre-op	68.7 (22.00	69.4 (21.8)	0.13 (0.9)
Score on discharge	60.5 (20.4)	58.9 (20.3)	-0.34 (0.74)
Score at 6 weeks	65.4 (15.2)	60.6 (18.9)	-1.21 (0.23)
Score at 12 weeks	69.9 (17.4)	66.0 (21.5)	-0.86 (0.40)
Difference pre-op to DC	-8.2 (23.2)	-10.5 (25.6)	-0.06 (0.96)
Difference DC to 6 weeks	+4.9 (17.1)	+1.7 (18.5)	0.78 (0.44)
Difference 6 weeks to 12 weeks	+4.5 (16.9)	+5.4 (16.6)	0.24 (0.81)
Emotional score			
Score pre-op	47.3 (48.4)	47.5 (44.4)	0.02 (0.9)
Score on discharge	34.6 (46.4)	24.9 (40.8)	-0.34 (0.74)
Score at 6 weeks	37.9 (45.2)	36.9 (46.3)	-1.21 (0.22)
Score at 12 weeks	56.0 (46.9)	39.6 (45.0)	-0.86 (0.39)
Difference pre-op to DC	-12.7 (64.4)	-22.6 (25.6)	-0.06 (0.95)
Difference DC to 6 weeks	+3.3 (17.1)	+12.0 (18.5)	0.78 (0.44)
Difference 6 weeks to 12 weeks	+18.1 (16.9)	-0.3 (16.6)	0.24 (0.81)
Social Functioning			
Score pre-op	63.3 (29.4)	48.3 (34.4)	-2.15 (0.03)*
Score on discharge	24.4 (26.7)	13.0 (16.7)	-2.28 (0.02)*
Score at 6 weeks	42.1 (28.1)	32.6 (24.6)	-1.6 (0.12)
Score at 12 weeks	54.6 (31.9)	45.3 (29.7)	-1.32 (0.19)
Difference pre-op to DC	-38.9 (33.2)	-35.3 (38.5)	0.82 (0.42)
Difference DC to 6 weeks	+17.7 (28.1)	+19.6 (22.6)	0.30 (0.76)
Difference 6 weeks to 12 weeks	+12.5 (26.7)	+12.7 (25.5)	0.03 (0.97)

*Statistically significant difference; DC= discharge

Comparison of Health Related Quality of Life

General Health Status

There were no statistically significant differences pre-operatively, at 6 weeks or at 12 weeks for General Health Status Factor. The mean values for each of group are presented in table 3.59.

On discharge the EEN group reported a mean higher score when compared to the STD group (50.3 (SD 20.3) versus 47.9 (SD 17.9)). The STD group deteriorated more post-operatively as compared to the EEN group (mean deterioration –11.5 (SD 21.8) versus –5.5 (SD 22.7) N.S). However, the EEN group deteriorated more post discharge as compared to the STD group (-2.5 (SS 18.4) versus +2.0 (SD 15.2) NS). Both groups showed improvement between 6 ands 12 weeks.

Physical Function

The groups had differences in mean pre-operative scores for physical function. The score for the STD group was higher than the EEN group (58.5 (SD 27.9) versus 67.2 (SD 28.6)). The difference did not reach statistical significance (t=1.38; p=0.172). The mean values for each of group are presented in table 3.59. There were no statistically significant differences in mean scores on discharge, 6 and 12 weeks.

Both groups had a large deterioration in physical function post-operatively; mean deterioration in scores was –25.1 (28.9) for the enteral group and –31.5 (SD 28.7) for the standard group. Both groups reported an improvement in physical function post discharge, with the EEN group improving more quickly than the STD group. However, neither group returned to the level of physical function as reported pre-operatively.

Vitality

The patients reported differences in pre-operative scores for vitality. The mean score for the EEN group was higher than the STD group (56.7 (SD 29.4) versus 50.4 SD 28.1)). The difference between the groups pre-operatively did not reach statistical significance (t=-0.405; p=0.687).

The deterioration in mean scores suggests that all patients reported a loss of vitality whilst hospitalised. Both groups reported their mean lowest score for vitality on discharge. The STD group had a mean lower score on discharge as compared to the EEN group. The difference did not reach statistical significance (t=-1.63; p=0.107). The mean values for each of group are presented in table 3.59.

The mean change in scores in both groups from pre-operative to discharge was similar. Following discharge, both groups reported an improvement in vitality; the improvement was slightly quicker in the STD group, as compared to the EEN group.

Physical Role

There were no statistically significant differences between the two groups on discharge, at 6 weeks and 12 weeks. The enteral feed group reported a slightly higher mean score at baseline (29.3 (SD 43.3) versus 25 (SD 41.2)). The scores pre-operatively for physical role when compared to other HRQOL factors were 'low' in both groups. The mean values for each of group are presented in table 3.59.

As expected following major resectional surgery, scores deteriorated after surgery. The scores on discharge were very 'low' for both groups with the standard group having a mean score of 0.69 (SD 4.2) and the EEN group having a mean score of 4.4 (SD17.9). Mean scores improved in both groups post discharge until 6 weeks but then both groups showed deterioration after 6 weeks to 12 weeks. The deterioration was greatest in the STD group. Mean scores were lower at 12 weeks than pre-operatively in both groups. This suggests that physical function takes longer to recover post discharge than other HRQoL factors.

Bodily Pain

The patients reported different mean pre-operative scores for bodily pain. The EEN group had a higher score as compared to the standard group.

The mean scores for both groups decreased during hospitalisation. This represents more bodily pain. This is to be expected following major surgery.

Neither group showed a significant improvement in pain at 6 weeks, with scores only slightly higher than on discharge. However, the EEN group showed an improvement between 6 and 12 weeks reporting less pain as compared to the STD group. The scores for the groups were statistically different at 6 and 12 weeks with the EEN group reporting mean higher scores, indicating less pain. The mean values for each of group are presented in table 3.59.

Mental Score

The mean scores for mental score were similar pre-operatively, on discharge, and at 6 and 12 weeks. The mean values for each of group are presented in table 3.59. The scores on discharge reduced for both groups, however, the decrease appeared to not be as marked as noted with other factors. Scores at 6 weeks remained similar as on discharge, with a reported slight increase in the enteral nutrition group. Scores at 12 weeks in the enteral nutrition group returned to near baseline scores, with continued improvement noted in the standard group almost returning to baseline scores.

Emotional Score

There were no statistically significant differences between the two groups pre-operatively, on discharge and at 6 and 12 weeks. The mean values for each of group are presented in table 3.59. Mean scores in both groups deteriorated between surgery and discharge, with the STD group showing more deterioration on discharge as compared to the EEN group.

Post discharge the STD group reported a more rapid improvement as compared to the EEN group; however, this resulted in similar scores in both group at 6 weeks. After 6 weeks, the standard group did not demonstrate any further improvement. The EEN group however continued to improve, with the mean score improving to be greater than pre-operative score.

Social Functioning

The mean scores of the groups were statistically different at baseline with the enteral nutrition group reporting a mean higher score (63.3 (SD 29.4)) as compared to the STD group (48.3 (SD 34.4)), t=-2.15;p=0.035). This may be a chance finding but the statistically significant difference in baseline scores needs to be considered when making inferences about the results of the RCTs' primary outcome.

The mean values for each of group are presented in table 3.59. Both groups reported a large deterioration in social functioning scores between surgery and discharge. Scores improved in both groups post discharge until 6 and 12 weeks. The difference in the mean scores was not statistically different. Mean scores did not return to that of baseline by 12 weeks.

3.7 Summary of Chapter

This chapter has provided the results of an early analysis of an RCT. The results of the primary outcome suggests that the null hypothesis may be refuted and suggests that EEN delivered via a feeding jejunostomy within 12-24 hours post-operatively to patients undergoing major resection of upper gastrointestinal malignancy, may led to a reduction in length of hospital stay.

This chapter has also reported the results of the secondary outcomes, in summary:

1. Early Enteral Nutrition may reduce the development of major complications. The most noticeable reduction was in infective complications.

2. The Early Enteral Nutrition group had fewer readmissions between discharge and 6 weeks and between 6 weeks and 12 weeks post discharge as compared to the standard group.

3. Early Enteral Nutrition was safe and feasible for patients undergoing major resection surgery, as reported by no tangible differences between the two groups in terms of the development of minor complications.

4. The Early Enteral Nutrition group had marked improvements in nutritional status, as compared to the Standard group, post-operatively.

5. There were no statistically significant differences between the two groups for health-related quality of life; however there was a trend to an improvement in the enteral nutrition group.

6. Early enteral nutrition provided a potential cost saving of £1,241.06 (£828.36-£5,315.40) per patient if delivered within 12 hours of leaving the operating theatre, as compared to patients who received standard post-operative management.

The following chapter will discuss the results of the RCT in the context of the previously reported literature. It will also discuss the generalisability of the RCT and options for implementation of the trials' results.

4. Discussion

4.0 Introduction

This aim of this study was to compare EEN with STD management in the post-operative management of patients undergoing major UGI resection for cancer. Previous surgical clinical nutrition trials have not provided sufficiently robust evidence to determine which approach is better.

The current study was conducted as a RCT, the 'gold standard' for determining clinical efficacy and efficiency in healthcare treatments. This chapter will firstly discuss the trial design, the main findings will then be discussed in comparison with the relevant literature and in the final section recommendations will be made for further research.

4.1 Trial Design

Upper GI resection for malignancy is a complex healthcare intervention with numerous extraneous and prognostic factors. It was therefore decided that the RCT was the most suitable trial design. The current RCT was a prospective multi-centre, randomised, pragmatic clinical trial. Pragmatic trials mimic clinical practice, compare two different healthcare interventions and use robust randomisation techniques with the aim of limiting bias.

As discussed in section 1.7.4 random allocation aims to reduce bias, by reducing the effects of extraneous variables so that the differences in outcome observed, between the randomised groups are due to the intervention.

The trial was initially single centred but due to relatively slow patient recruitment rates in the first year, further funding was obtained and the number of trial centres increased to 4 over the course of a year. These 4 centres form part of the regional UGI Cancer network. By involving patients from several centres, any conclusions have a broader, more representative base, than can be achieved in a single centre.

4.1.1 The Hospital Centres

The four hospital centres had 5 consultant surgeons with patients eligible for inclusion in the study. There were 4 oesophago-gastric surgeons and 1 hepatobiliary surgeon. Stratification was performed per hospital centre, as it was perceived that different pathways of care might occur in each centre. One example is the use of critical care management in the different centres. In centre 3, the patients typically stay in critical care for up to 5-7days post-operatively. In contrast, centre 1 would traditionally keep patients in critical care for 24 hours. This has potential implications for trial outcomes.

The use of needle catheter jejunostomy (NCJ) was not routine in all 4 centres prior to starting the RCT. Therefore, measures were put in place for training staff regarding both the insertion and post-insertion care of the NCJ. These were the responsibility of the PI in conjunction with the lead surgeon at each centre.

The number of clinical ward based dietitians was also minimal in 2 of the centres. This resulted in several logistical problems, such as day-to-day management of the enteral feeds. Additional funding was obtained to allow allocation of a small amount of local dietetic time to administer the enteral feeds. Close liaison, education and training of the dietitians were required to ensure compliance with the study protocol.

4.2 Trial Progress

4.2.1 Sample Population

This RCT focused on patients with UGI cancer undergoing major resections with curative intention. It is well documented that UGI surgery has high morbidity and significant mortality [19, 39, 153] in addition, these patients are unable to tolerate food and fluid orally for typically up to 10 days after surgical resection [59, 60]. Therefore, any supportive intervention that could enhance recovery and reducing the risks would be welcome.

The study sample median age was 69 years (58-77 years) which is similar to that reported in the National Cancer Statistics in 1999 [102] (median age 64; 58-72 years). The gender distribution was, as expected, approximately twice as many men than women in gastric and oesophageal cancer. The incidence of pancreatic cancer was similar in men and women.

4.2.2 Recruitment

As all participating consultant surgeons were actively referring patients to the study, it is assumed that all eligible patients were approached regarding recruitment into the study. A total of 139 patients were recruited to the trial. The average number recruited per month was 4.34 patients, below the anticipated recruitment of 6.4 patients/month outlined in the original protocol. Slower than anticipated accrual rates have also been reported in other RCTs [550].

It is not clear why recruitment was slower in the present study. It may be that fewer patients presented to their GP with symptoms of UGI cancer during the RCT, or that fewer patients were suspected to have UGI cancer by their GP and referral for specialist tertiary intervention in hospital was not made. However, there is no reason to assume that these occurred, especially in the light of a raised public awareness of the symptoms of cancers in recent years and the introduction of Cancer Standards for Wales (Welsh Cancer Intelligence and Surveillance Unit, 2005, Welsh Assembly Government)[617].

Another possibility is that the figures used as a basis for calculating the anticipated accrual rate were incorrect, maybe due to changes in clinical coding. Finally, the slower accrual rates maybe a result of fewer patients having surgery compared to several years ago when the trial was planned. This may be the result of improvements in radiological imaging detecting patients with non-curable disease who previously would have been submitted to surgery. This will be discussed later in this section.

The consent rate was 82.2%. Similar consent rates have been reported in other cancer trials [620]. There were no statistically significant differences between the

patients who did not consent with the patients who did consent (table 3.3). Information as to why the patients did not consent was not collected, as this was considered inappropriate and unethical. Several hypothetical reasons are detailed below. It may be that:

1. The patients and/or their relatives did not want to be burdened with more information and decisions at a time when they have just received a suspected diagnosis of cancer

2. They were already participating in a clinical trial

3. The Consultant Surgeon who first discussed the RCT with the patient may have influenced the patients' decision. However, this is unlikely, as all 5 Consultants had appeared to have clinical equipoise regarding the trial.

Of the 139 patients who gave consent, 102 patients were subsequently randomised, as 37 patients were deemed palliative at operation. The majority of these palliative patients were pancreatic. This gives credit to the state-of-the-art radiology that accurately diagnosed the oesophago-gastric patients. However, radiology appears not to accurately predict the likelihood of pancreatic patients being able to have a curative resection.

It was the view of the operating surgeon that pancreatic tumours often involve the superior mesenteric vein or portal vein. Unfortunately, this is often only discovered during the dissection stage of the operation, as the adherence of the pancreas to the vessels is not always detectable by current radiological imaging (Puntis, personal communication, 2007). Therefore it was inevitable that a proportion of the patients recruited would not be randomised following laparotomy, as they had a palliative (R1) operation.

Sixty patients were randomised to receive early enteral nutrition and 42 patients were randomised to receive standard management. There was an imbalance of 18 patients between the two groups when the MCRCT closed for the early analysis for this thesis; this can be explained by the block randomisation. There were four hospital sites and each site was stratified and had its own set of

randomisation envelopes. The randomisation was in blocks of 30. The reasons for this are presented in section 2.2.3.1.

The number of patients recruited from centre 1 was 85; therefore, this centre used 2 complete blocks of 30. Of the 3rd block there were 5 randomisation envelopes left. Centre 2, 3 and 4 did not complete a full series of randomisation envelopes. This is illustrated in table 4.1.

Because of the slower than expected accrual, the RCT continued to recruit patients following the 'cut off' for data analysis for this thesis. It is therefore likely that the allocation of patients to each randomisation group will become more balanced as the trial continues to recruit.

Table 4.1 Recruitment and use of randomisation envelopes for patients in each of the Randomisation groups per hospital Centre.

Hospital Centre	No. of patients recruited	No. of completed Randomisation blocks used	Randomisation envelopes remaining in block
Centre 1	85	2	5
Centre 2	3	0	27
Centre 3	14	0	16
Centre 4	0	0	0

Importantly, the imbalance of patients allocated to each group was not sufficient to affect the power of the study to refute the primary hypothesis. However, several of the secondary endpoints were not statistically significant, thus recruitment continued after the data analysis for this thesis, in order to ensure the power of the study.

4.2.3 Baseline Comparison of the Two Randomisation Groups

The two-randomisation groups were equivalent for comparison in this RCT for age, pre-operative tumour stage, frequency of use of neo-adjuvant chemotherapy and POSSUM scores. Intraoperative factors such as operation duration and blood loss were also comparable. Interestingly, the two groups were not comparable for all of the factors on the HRQoL. The scores for social function were significantly different. The impact of this on the primary outcome is discussed in section 4.3.6.

It could be argued that having a heterogeneous group of patients (pancreatic and oesophago-gastric) is not ideal. The operations are obviously different, but the duration of the operation, the magnitude and complexity of the surgical procedures and the risk of post-operative mortality and morbidity are considered comparable [19, 39, 153].

The differing types of surgical procedures used are only relevant if the baseline groups are not similar for the distribution of these procedures. The study by Heslin *et al* (1997) [503] had a disproportionate number of oesophageal and pancreatic patients in each arm of the study. The difficulty is that these differences tend to become apparent only after closing the study and analysing the results.

Within each arm of the current RCT, there were no differences between the numbers of patients undergoing each procedure in each randomisation group. Therefore, the groups were considered sufficiently equivalent for meaningful inferences to be made.

Baseline Comparison of the Randomisation Groups for Pre-operative Nutritional Parameters

No differences were found in the pre-operative nutritional status of the enteral nutrition group compared to the standard group. This section will discuss the results from the current study of the pre-operative nutritional parameters in line with the previous literature in this area.

The total study sample had a pre-illness median Body Mass Index (BMI) of 27.5. The median BMI at presentation had dropped to 25.4. This is not surprising, as 36% of the total study sample had lost more than 10% of their pre-illness weight in the 3 months prior to surgery. This is similar to findings by Windsor and Hill (1988)[282] who reported that 45% of cancer patients in their study had lost over 10% of their pre-illness weight at presentation. The extent of the percentage weight loss and the timescale of the percentage weight loss are important. Studely (1936) [9] reported that surgical outcome was negatively influenced by increasing pre-operative percentage weight loss. This was also the finding of Roy *et al* (1985) [222] who concluded that a weight loss of >6% of usual body weight more accurately predicted morbidity and mortality in surgical patients than other prognostic indices.

Based on the percentage weight loss, the current study sample had a weight loss, which was clinically relevant. As discussed in section 1.3, weight loss *per se* represents changes in body composition, with all body stores, i.e. glucose, fat, fluid and protein stores being affected. Unlike glucose and fat, there is no inert protein store. Therefore, any depletion of body protein stores will originate from lean body tissues and progress to altered organ function. This alteration, will become apparent at certain percentage weight losses [236] (table 1.4.1).

The use of different criteria to define malnutrition, as well as the inclusion of patients with differing stages of disease prevents the true comparison of the nutritional parameters between studies. Any future study should use nutritional parameters that are reproducible and reliable to aid comparisons between studies. Several studies [8, 94, 176-178, 181] have reported the incidence of malnutrition in UGI cancer. Two studies [177] [178] used unintentional preoperative weight loss to define malnutrition. These two studies report an

incidence of malnutrition of 57% and 58% respectively. If the same criterion was used in the current RCT sample, a similar incidence is evident, 51% (N=49). Table 4.2 shows the pre-operative nutritional data from this RCT in line with analyses performed in other clinical nutrition trials.

When interpreting the incidence of malnutrition it is important to remember that all patients in the current study had a stage of disease that was potentially curative by surgery. This is not the case in several other studies, which included patients receiving both palliative and curative intent surgery and modalities.

For example, the DeWys (1980) [176] study examined patients when their disease was beyond the scope of surgery. This is important, as the stage of disease has been reported to be one of the factors contributing to protein calorie malnutrition [180].

Table 4.2 A comparison of the baseline results of the incidence of malnutrition of this RCT compared with previous published studies

Author (year)	Criterion used to Define Malnutrition	Incidence of Malnutrition in studies of GI cancer patients	Incidence of malnutrition in current study if previous studies criterion is used
Persson *et al* (1999) [8]	Subjective Global Assessment (SGA)	UGI cancers 80%	Not recorded in this RCT
DeWys *et al* (1980) [176]	Weight loss > 5% in 6 months	Pancreatic cancer 83% Oesophageal cancer 87% Gastric cancer 65%	Total sample 51%
Riccardi and Allen (1999) [94]	10% weight loss over 4 months	UGI cancers 70%	Total sample 36% (over 3 months)
Daly *et al* (2000) [177]	Involuntary weight loss	Oesophageal cancer 57%	Total sample 51%
Martin *et al* (1999) [178]	Involuntary weight loss	Oesophageal Cancer 58%	Total sample 51%
Rey-Ferro *et al* (1997) [181]	Nutrition Risk Index (NRI) less than 97.5	Gastric Cancer 63%	Total sample 18.5%
Thoresen *et al* (2002) [184]	Involuntary weight loss Weight loss > 10% BMI >18	All GI cancers 83% All GI cancers 63% All GI cancers 30%	Total sample 51.1% Total sample 36% Total sample 5.2%

As mentioned, 51% of the sample population had lost weight pre-operatively. The reason for this was presumably due to the reported reduced calorie intake (1450 calories/day) prior to admission. Eighteen patients (18.8%) from the study population were eating less than 1000 calories per day. The recommended calorie intake (based on Elwyn (1980)) [572] is 30 calories per kilogram /day. The total study population was consuming less than the recommended calorie intake per day as measured by this recommendation.

Similar results were evident for protein intake. The mean protein intake for the total study population was 58 grams per day. This equates to 0.8 g protein per kilogram per day. The recommendation for non-hypermetabolic patients is 1 gram per kilogram/day. Forty patients (42%) of the total study population were eating less than 50 grams protein per day. This is clinically relevant as a study by Shaw-Stiffel (1993) [344] suggested that reduced oral intake prior to surgery may lead to increased risk of complications. This correlation was not performed for presentation in this thesis, however, as this was not one of the objectives.

This study concluded that 25% of pre-operative patients had a reduced appetite, which is in line with the study by Murray (1979)[188]. One criticism of recording appetite is that it is very subjective. In this study patients were asked to recall how their current appetite compared to their usual appetite. The author appreciates that difficulties in recollection could have skewed the results. Nevertheless, it is still interesting that 25% of the total study population had anorexia.

4.3 Discussion of Outcomes

Upper GI surgery is associated with a high morbidity [19, 39, 153] which may be influenced by the patients' physiological condition. Patients undergoing major UGI surgery are often malnourished prior to admission for their surgery [177] [178]. The patients in the current study were generally malnourished reflected by a median pre-operative weight loss of 6.3%.

In section 1.3 the deleterious effects of malnutrition on physiological condition were discussed. Pre-existing malnutrition deleteriously affects surgical outcome [5, 7, 10, 11, 170, 327, 336-338]. It could therefore be assumed that patients in the current RCT had a problematic post-operative recovery due to malnutrition. Logically, the use of nutritional support, which is designed to prevent and correct nutritional deficiencies and malnutrition [40], should optimise surgical outcome. However, few clinical nutrition trials have provided a consensus on whether the use of nutritional support post-operatively is beneficial to clinical outcome.

Patients undergoing major UGI surgery tend to have a long period of nil by mouth before recommencing 'adequate' oral diet [70]. This is because of reduced satiety and impaired gastric function [70]. Ryan *et al* (2006) [70] suggested that the use of EEN via a NCJ after UGI surgery allows time for the patients' appetite to recover, ensuring adequate nutritional intake is delivered. This is particularly important in a patient who develops complications, which can markedly delay the onset of oral intake.

However, surgeons may argue that the use of a NCJ purely to provide adequate nutrition whilst appetite improves or in the event of a patient developing complications is not justified. This is especially so, when the clinical efficacy and effectiveness of EEN is not proven in the context of a RCT. Many surgeons prefer to use TPN in the surgical setting. This is because of lack of robust clinical trials and fear of EEN related adverse effects, inducing complications [532].

Studies indicate that EEN is more 'physiological' than TPN, preserving GIT function and preventing GIT structural alterations induced by starvation and or

injury [621-625]. Alongside, EN is feasible immediately after major surgery, as small intestinal peristalsis recovers 6-8 hours after surgical manipulation [384], the direct passage of nutrients in the GIT lumen early after major surgery or injury, increases splanchnic blood flow and stimulates GI immune system all aiming to assist in improving clinical recovery [621-625]. EN is also less expensive than TPN [40]. Yet, as detailed in section 1.5, once again these benefits are not reflected in a consensus for the use of EEN.

The current RCT aimed to compare standard post-operative management with the immediate delivery of early enteral nutrition via a needle catheter jejunostomy within the framework of a pragmatic RCT. The next section will provide a summary of the main outcomes of the current RCT and then discuss these findings in the context of previously published work.

4.3.0 Summary of Outcomes

Primary outcome
This analysis of this trial has indicated that:

1 Early Enteral Nutrition delivered via a feeding jejunostomy within 12-24 hours post-operatively to patients undergoing major resection of upper gastrointestinal malignancy, may lead to a reduction in length of hospital stay as compared to patients who continued to receive standard hospital management. The reduction of LOHS was 4 days with the use of EEN.

Secondary Outcomes
1. Early Enteral Nutrition may reduce the development of major complications. The most noticeable reduction was in infective complications.

2. Early Enteral Nutrition may lead to fewer readmissions between discharge and 6 post-operative weeks, and between 6 weeks and 12 weeks, as compared to the standard group.

3. Early Enteral Nutrition was safe and feasible for patients undergoing major resection surgery.

4. The Early Enteral Nutrition group appear to have a marked improvement in nutritional status, as compared to the Standard group, post-operatively.

5. So far, this analysis has indicated that no statistically significant differences between the two groups exist, for health-related quality of life.

6. Early enteral nutrition may provide a potential cost saving of £1,241.06 (£828.36-£5,315.40) per patient if delivered within 12 hours of leaving the operating theatre, compared to patients who received standard post-operative management.

4.3.1 Primary outcome

Early enteral nutrition delivered via a feeding jejunostomy within 12 hours post-operatively to patients undergoing major resection of upper gastrointestinal malignancy, may lead to a reduction in length of hospital stay when compared to patients who received standard hospital management

This early analysis has indicated that the use of EEN maybe superior to STD management in improving a patient's clinical outcome as defined by a shortened LOHS.

The Per Protocol analysis concluded that the median LOHS for the STD group was 20 days (14.75-28 days) compared to 16 days (IQ range 13-22 days) in the EEN group. The difference between the groups was statistically significant (U=822.50, p=0.021). The intention-to-treat analysis concluded the same median difference, but the results were approaching statistical significance (U=999.8; p=0.068).

Several EN versus STD management RCTs have used LOHS as a primary outcome measure. Of these, five have also concluded that EN reduced LOHS [12, 15, 16, 483, 518]. These studies, however, failed to reach statistical significance, presumably due to their small sample sizes. Thus, to date the literature for true comparison is sparse. There is one meta-analysis (studies N=11) of EN versus STD management, comparing patients undergoing all types of major GI surgery. This analysis, Lewis *et al* (2001)[17] concluded that EN reduced LOHS by 1 day. Therefore, the findings of a 4 day reduction in LOHS is four times that found in the meta-analysis and has major implications for patient care and the NHS. There have been no Cochrane systematic reviews to date in this field.

4.3.1.1 The Definition of Length of Hospital Stay

Definitions of outcomes are very important in clinical trials. Readers must fully understand what criteria were used to determine outcome measures. By clearly defining what criteria the investigator used, readers are then able to make their own interpretation of the results. The precise definition of LOHS was therefore

vital. Collins *et al* (1999) [564] (page 255), defined LOHS as, 'the time from when the patient underwent the index operation to when discharged home'.

This definition does not take into account that patients often remain in hospital for many reasons other for than surgical and medical indications. Currently in the UK, with separate funding streams for healthcare and social care, delays in agreeing social care packages can delay a patient's discharge from hospital even when they are medically fit for discharge. Without taking the external factors that can affect LOHS into account, misleading results can occur.

It was for this reason that for the purpose of this RCT, LOHS was defined as the time from the index operation to when the patients were declared medically fit for discharge. This definition can also be criticised without robust discharge criteria being available. The discharge criteria for this RCT are presented in section 2.1.6.2.

To date, there remains no consensus for a definition for LOHS (Blazeby, J, personal communication, 2008). One clinical trial by King *et al* (2005) [626] used length of hospital stay as a primary outcome. A total hospital stay including post-operative hospital stay, convalescence stay and readmission stay supported this as a secondary outcome. Any future clinical trials in this field should aim to report both methods of defining LOHS. However, it is important to note that this method may limited when conducting multicentred trials, as each institution may have differing administrative procedures and management strategies for bed management, for both pre and post operative stay, making comparison across institutions more complex.

LOHS can be affected by many factors, including age, pre-operative physical status score, intra-operative factors such as blood loss, and duration of time in theatre, type of surgical procedure and the presence of co-morbidities. These factors have all been associated with prolonged LOHS [565, 566]. For the current RCT, pre-operative demographic and operative factors were comparable at baseline. Likewise intraoperative factors were comparable at baseline (Tables 3.4-3.6). Interestingly, there was a baseline imbalance for social function, one of the eight factors on the SF36. This imbalance could be very important when interpreting the primary outcome. The higher mean score in the EEN group may

have contributed to the shorter hospital stay [627]. This will be discussed later in this section (section 4.3.6).

To summarise, the use of length of hospital as a primary outcome can be criticised. It can be considered to be subjective and open to the risk of observer bias. However, length of hospital stay was considered to be the most appropriate primary endpoint, for true comparison with the previous literature [12, 13, 17, 503], when the trial protocol was developed in 2002. What is imperative is that researchers clearly outline the definitions of both primary and secondary outcomes used in clinical trials. This allows the reader to make inferences about the validity and relevance of the outcomes for implementation in their own clinical practice.

4.3.1.2 Readmission to hospital

The use of LOHS as a primary outcome measure can be criticised if patients are discharged back into the community with complications. Information on the number of hospital readmissions is essential to support the result of the differences in length of hospital stay. Any RCT that reports LOHS as a primary outcome should report the number of patients requiring readmission to hospital. It is clearly not beneficial for a patient to be discharged early from hospital, to be readmitted at a later date. The EEN group had fewer readmissions between discharge and 6 weeks (7.6%) compared to the STD group (14.3%); and also fewer readmissions between 6 weeks and 12 weeks (1.9% versus 4.8%). Despite not being statistically significant the findings are nevertheless relevant.

Readmission to hospital may have a profound psychological effect on patients, affecting their HRQoL. This RCT has demonstrated that the EEN group had approximately half the readmission rate than the STD group. If these figures are annualised, then the cost saving would be considerable to the NHS. To our knowledge, no other published RCT in UGI cancer patients undergoing surgical resection has reported the impact of EEN versus STD on readmission rates to hospital.

4.3.2 Secondary Outcomes

Secondary Outcome 2: Early Enteral Nutrition may reduce the development of hospital acquired major complications when compared to patients who received standard post-operative management.

Upper GI surgery has a high morbidity and mortality associated with it [19, 39, 153]. Therefore, it is anticipated that a proportion of patients will develop major complications. It is not clear why certain patients develop complications and others do not. The development of multiple complications suggests that a health care organisation maybe providing an inferior service [564]. Collins *et al* (1999) [564] stated that patients who develop complications are more costly. Thus, any intervention that can reduce the development of complications is beneficial for patients and the healthcare organisation.

The current analysis of this RCT suggested that EEN reduced the development of major complications compared to the use of STD management in patients undergoing major resection for UGI cancer. The STD group developed three times more major complications in hospital, compared to the EEN group (1.64 versus 0.54 respectively).

The reduction of major complications was particularly striking for infective complications with the EEN group developing significantly fewer chests and wound infections. Other RCTS have reported similar results [46, 312]. Alongside this the EEN group had improved wound healing rates, presumably related to the fewer wound infections. Four patients (9.5%) in the STD group compared to one patient (1.9%) in the EEN group had impaired abdominal wound healing, characterised by a gaping abdominal wound of more than 3 cm. The results of this study are similar to findings by Schroeder *et al* (1991)[16].

Anastomotic healing rates were also remarkably different for the two groups, with the EEN group having improved anastomotic healing. This supports the findings

of four studies [68, 532, 533, 628] and one meta-analysis [17] which suggested that a jejunal infusion of EEN benefits anastomotic healing

To our knowledge, this analysis is the largest series of patients comparing EEN versus STD management in patients undergoing major resection for UGI cancer, to suggest that EEN maybe beneficial in anastomotic healing rates. The reduction in wound healing problems in particular anastomotic healing has major implications. Anastomotic leaks are a major concern for surgeons and patients, because of the increased LOHS and mortality associated with them.

Gastric emptying was improved in the EEN group. This was surprising as a study by Martignoni *et al* (2000) [424] concluded that EN delivered via a jejunostomy into the small intestine decreased gastric emptying. However, the numbers are small 7.3% (3/42) versus 1.8% (1/56) so meaningful conclusions are hard to draw.

Complication Ratio

McAleese and Oldling-Smee (1994) [567] introduced the concept of complication ratios. Complication ratios refer to the ratio to which LOHS will be increased if complications are developed by a patient. McAleese and Oldling-Smee stated that the development of any major surgical complications increased a patient's average LOHS by 3.3 to 4.4 times, to that of a routine hospital stay. The use of complication ratios were used in the current RCT to compare the severity of the complications developed in each randomisation group. The results of the current RCT suggest a lower overall complication ratio of 1.39 for the EEN group and 1.55 for the STD group (table 4.3).

There are several possible explanations:

1. The complications developed were more severe in the study by McAleese and Oldling-Smee [567]

2. The LOHS were typically shorter in the McAleese and Oldling-Smee study [567] therefore the complication ratio appears higher.

3. The definition of LOHS used in the McAleese and Oldling-Smee study [567] was not clear. It is assumed that the authors used the actual LOHS, which, as discussed, can be misleading.

The differing outcomes of the complication ratio for the current study and the study by McAleese and Oldling-Smee [567] demonstrate the importance of detailed reporting of outcomes. The failure to adequately define outcomes allows the reader to make inferences about the results. Having stringent definitions of what constitutes a complication ensures meticulous data collection, promoting reliability and validity of the study and its results.

Table 4.3 Comparison of Complication Ratios of the current study with the Complications Ratios published by McAleese and Oldling-Smee (1994) [567]

Type of Complication	Standard Group Mean ratio (LOHS**)	Enteral Group Mean ratio (LOHS**)	McAleese and Oldling-Smee Ratios
All major complications	1.55 (24.18)	1.39 (20.19)	3.3-4.4
Infective Complications	1.50 (23.46)	1.28 (18.6)	
Wound Infection	1.66 (25.9)	1.14 (16.6)	2.43
Chest Infection	1.33 (20.8)	1.42 (20.6)	1.99
Non Infective complications	1.35 (21.1)	1.29 (18.7)	3.4
Delayed gastric Emptying	1.41 (22.1)	1.28 (18.6)	1.99
Pleural effusion	1.81(28.3)	1.66 (24.1)	-
Chylothorax	0 (0)	1.4* (20.3)	3.4
Anastomotic Leak	1.9 (29.7)	0 (0)	1.88
Open Abdominal Wound	1.38 (21.6)	2.45* (35.6)	1.99
Respiratory Failure	1.6 (25.0)	0.96 (28.5)	-

* Only 1 patient in this group, therefore interpretation is limited

** The figure in the brackets refers to the predicted LOHS that would occur if the complication were developed. The LOHS used for the calculation of the complication ratios is the actual median LOHS for the STD and EEN group patients who did not develop a complication

Complications present on the day of discharge

At the cut off for this early analysis, fewer patients were discharged with complications in the EEN group compared to the STD group, six patients (11.1%) in the EEN group vs. 16 patients (33.3%) in the STD group) (Chi square= 8.56; p=0.0001; CI >0.0001-0.045). This is manifested in a trend

towards improved HRQoL in the EEN group reported on the day of discharge. Discharging patients into the community with complications has implications for primary care, community nursing, extra prescriptions for drugs or dressings, and extra visits to General Practitioners. Also, surgical complications may lead to a patient feeling socially isolated, as they may be unable to return to their normal activities of daily living, being more dependent on carers.

To our knowledge this is the first indication that the use of EEN versus STD management in patients undergoing major resection for UGI cancer may reduce the incidence of surgical complications in patients being discharged from hospital into the community.

4.3.3 Mechanisms of Early Enteral Nutrition Induced Benefits

The current study so far, has demonstrated a surprisingly clear improvement in the primary outcome and a reduction in major complications in the EEN group. However, there is almost certainly scope for refining the nutritional intervention to achieve the maximum benefit for patients with minimal risk and cost. In order to do this, efforts must be made to understand the details of the mechanism whereby nutritional interventions have their effect. It is becoming clear that these mechanisms are complex, interlinked and interdependent, and require extensive future study, which will be discussed in the next section.

Correction of Malnutrition

The use of EEN in improving clinical outcomes may be as simple as correcting the deleterious effects of malnutrition, or preventing these deleterious effects from occurring. Studies have illustrated how malnutrition deleteriously affects surgical recovery [5, 7, 155, 170, 327, 337, 338] and how malnutrition has a harmful affect on physiological function (section 1.4.2). Nutritional support is considered the only evidence-based modality capable of correcting the effects of malnutrition [40]. However, this would then infer that the use of any method or route of nutritional support (i.e. TPN or EN) is comparable, but this is not the case (table 1.6.3).

Enteral Nutrition and the Modulation of the Immunological Response

EN and TPN are not comparable in improving clinical outcome [52-58, 279, 359, 361, 381, 441, 474-476].

The superiority of EN centres on its role in regulating the immune response both systemically [49, 312-314, 371, 372] and intestinally via the stimulation of Peyers patch cells lining the small intestines [46, 47]. Coupled with this, EEN has a 'trophic' action on the small intestines improving GIT integrity, aiming to limit the translocation of bacteria into the systemic circulation [49, 313, 314, 372] (Section 1.5).

Therefore, the role of EEN in enhancing immunity may be central in improving clinical outcome. This may explain why the current RCT demonstrated a statistical significant reduction in infective complications in the EEN group.

Attenuation of the Catabolic Response

The current study used nitrogen balance as a surrogate marker of catabolism. A sub-section of the study population (N=44) had nitrogen balance studies. The difference between the groups was statistically significant; with all those in the STD group in a negative nitrogen balance on day 5 post-operatively compared to 11 patients (47.8%) in the EEN group (Chi 22.2; p=0.01). Eight patients (34.7%) in the EEN group were in a positive nitrogen balance on day 5. This is comparable to other studies in surgical patients [377-379, 483, 629].

Nitrogen balance is considered to reflect metabolic stress [268] a positive nitrogen balance is thought to indicate an attenuation of the APR. A positive nitrogen balance suggests a reduction in catabolism, optimising the free nitrogenous substrates available for wound healing and tissue repair.

The mechanisms as to why the EEN group had improved nitrogen balances are not clear, as these were not explored in the current RCT. Next the theoretical exploratory mechanisms will be detailed, all of which are interlinked. However, it will become evident that further studies are needed to substantiate these theories.

The EEN group actually received nutrients via the GIT. The STD group did not. Circulation of nutrients in the systemic circulation initiates a fed state response. Insulin production is increased, diminishing catabolism, and inhibiting gluconeogenesis. A study by Hochwald *et al* (1997) [378] supports this theory, demonstrating an approximate two-fold increase in insulin levels in patients who received EN when compared to patients who received TPN. This was mirrored by a protein sparing effect, an improved nitrogen balance and a significant impact on protein loss coupled with a reduction in endogenous fat oxidation. Thus patients had improved muscle and fat mass.

What this study does not explain, however, is why TPN failed to increase insulin production to the same degree; TPN would provide a systemic supply of nutrients, therefore should initiate a fed state response. This is apparent as insulin was produced in the TPN group in the Hochwald study. What is interesting is that insulin production and hence attenuation of the APR did not occur to the same degree as the EN group. Maybe enhanced insulin secretion requires a supply of nutrients via the portal vein from the GIT? Does the liver have a pivotal role in this mechanism? These possibilities require further investigation.

2. The role of EN has been described in modulating the inflammatory and immuno-modulatory response [373-376]. In the current RCT, the EEN may have suppressed the APR, as reflected by an improved nitrogen balance. [46, 47, 373].

The current RCT did not demonstrate any differences between the two randomised groups for two markers of the APR, albumin and CRP. This supports the finding of the study by Moore and Jones 1986 [483] who also used EN versus STD management in patients undergoing major emergency trauma surgery and reported no difference in these markers. However Peterson (1988) [374] suggested that EEN did improve serum albumin and decreased circulating levels of CRP.

There are possible explanations for the different findings in the studies. Firstly the current study and the Moore and Jones 1986 [483] study compared EEN

versus STD management. The Peterson 1988 [374] study compared EEN versus TPN.

Secondly, it may be that the current RCT did not collect the assays for CRP and albumin at the correct times to detect the sensitive fluctuation in these markers. With more frequent assays subtle changes may have been detected. The current RCT relied on routine blood sampling, as more frequent assays were not available due to cost pressures of the trial.

Fluid Balance

More patients in the STD group developed oedema than in the EEN group (N=15 (36.6%) versus N=4 (8%) p=0.0001). The STD group had a slightly higher cumulative positive fluid balance in the first post-operative week (+ve 5123 mls) compared to the EEN group (+ve 4053 mls). As expected the STD group had a mean higher volume of intravenous fluids administered in the first post-operative week compared to the EEN group. The slight difference between the two groups for fluid balance does not explain the marked difference between the two groups for the development of oedema.

Oedema has long been associated with deleterious clinical outcome in particular its negative impact on wound healing [255], thus the development of oedema was taken as an important surrogate outcome. The reduced oedema in the EEN group may have occurred for several reasons.

1. The enteral feed *per se* ensured a constant delivery of calories and nitrogen substrates that may have enabled adequate protein synthesis to maintain adequate blood oncotic pressure. However, as discussed previously, this was not reflected by marked changes in the serum albumin levels for the groups.

2. The EN may attenuate the acute phase response as reflected by an improved nitrogen balance in the EEN group. The APR alters fluid balance [255], causing fluid and electrolytes to be conserved. This is mediated by an endocrine response involving several hormones, including anti-diuretic hormone, aldosterone and rennin-angiotensin II system [630] which all lead to an increase in total body fluid volume. Concurrently, the release of inflammatory cytokines

and mediators such as IL-6 and TNF-alpha, act as vasodilators, increasing capillary permeability. The net result is increased fluid distributed into the interstitial space [255], the magnitude of which is proportional to the extent of the stress stimuli.

The RCT concluded that the groups did not have a markedly different fluid balance for the 1st post-operative week. However, both groups had a positive cumulative balance exceeding 4 litres. Studies have illustrated that optimal fluid balance is essential in post-operative surgical management [255, 631]. However, the fluid balance management of surgical patients is challenging.

The prescription of intravenous fluids tends to be the responsibility of the pre-registration house officers (PRHOs). The PRHOs will typically prescribe fluids based on the fluid balance chart, which is dependent on nursing records and documentation. The optimal prescription of fluids is dependent on a clear understanding of fluid balance by the prescribing doctor. The types of fluids used are critical, as the choice of colloids or crystalloid can radically influence clinical outcome [255, 632].

The issues surrounding the challenges of post-operative fluid management were highlighted in a survey by Lobo (2002) [631]. He concluded that current peri-operative fluid and electrolyte management in the UK is suboptimal. With only 16% of Consultants reporting that they felt their PRHOs had adequate knowledge in fluid management. As a consequence, only 30% of Consultants felt that postoperative patients received the appropriate amounts of water, sodium and potassium.

What is important is that fluid management needs to have more detailed attention and priority in the management of the surgical patients by clinical staff of all grades.

Prevention of Hyperglycaemia

A study [213] concluded that following surgery an insulin resistance type syndrome (similar to that seen in Type II diabetes) occurs, in the first few days

post-operatively. Therefore the delivery of exogenous glucose (via nutritional support) can accentuate an already elevated blood glucose level. This may increase the likelihood of infections and provides a sub-optimal condition for wound healing.

Supporting this theory are two studies which have shown an increased complication rates in patients who received TPN [469, 470]. It has been previously discussed that patients who receive TPN have a lower production of endogenous insulin when compared to patients who received EN [378]. Coupled with this, TPN infusions tend to have a higher glucose load compared to EN, which may accentuate blood glucose levels.

The glucose delivery for the current study was slow as the EN was started at 10-20 mls and increased by 10 ml/hour every 12-24 hours, with the aim of delivering full nutritional requirements by day 5 post-operatively. Therefore, it is assumed that the concentration of glucose delivered was not excessive in the first 48-72 hours. However, this study did not monitor blood glucose or insulin levels, so this cannot be confirmed.

Secondary Outcome 3:
EEN was safe and feasible for patients post-operatively as demonstrated by no measurable differences between the two groups in terms of the development of minor complications.

4.3.4 Feasibility of Enteral Nutrition

The use of EN in the immediate post-operative period is often blamed for the increased reports of nausea, vomiting, abdominal distension, cramps and diarrhoea often seen in post-operative patients. Several studies [64, 66, 70] [65, 69, 358, 524] have shown that EN is not responsible for these symptoms, moreover, these complaints do not interrupt the delivery of EEN.

This was the finding so far of the current RCT. The number of patients who had uninterrupted enteral feeding in the 1st week in the current RCT was 85.2% (N=46). The results of this RCT are presented in line with previous studies in table 4.4.

Table 4.4. The number of patients who had uninterrupted enteral feeding in the current RCT as compared to the previously published studies

	Uninterrupted Feeding for the 1st week post-op	Comments
This RCT	85.2 (14)	NCJ Feed commenced at 10ml/hr increased slowly* over 5 days
Biffi et al (2000)[64]	98.8 (79)	NCJ Feed commenced at 15ml/hr increased over 5 days
Ryan et al (2006)[70]	92 (13)	Colorectal patients
Braga et al (2002)[66]	70 (455)	NCJ Feed commenced at 15ml/hr increased slowly
Chin et al (2004)[65]	80 (64)	-
Sarr (1999)[69]	85 (425)	Used NCJ
Smith (1985)[358]	56 (14)	Foley catheter
DeGottardi[524]	82 (18)	N=26 developed catheter related complications

Jejunostomy Tube related Complications

The incidence of complications attributed to the needle catheter jejunostomy (NCJ) was 0% (N=0) in this early analysis of the current RCT. Other studies have reported the incidence of complications to be 0-40% [63-75]. The current RCT used the Fresenius *freka* NCJ that was inserted by one of the surgeons who conducted the main resection. The surgeons all reported that the zero complication rates were attributed to the technique of insertion of the NCJ. Therefore, the same dedicated surgeons using the same skilled technique was responsible for the very low complication rate.

However, this theory is refuted by one published cohort study [65]. This study by Chin *et al* (2004) had a complication rate of 12.9%. They used a dedicated surgeon for inserting the NCJ. DeGottardi (1999)[524] commented that it is the meticulous skilled insertion techniques and not just the use of a dedicated surgeon that was required to produce a low jejunostomy complication rate.

The type of feeding tube is also vital. As presented (table 1.6.6) there are a variety of tubes used in clinical studies, all with varying complication rates. Three studies [488, 503] [358] reported to use a Foley catheter as the jejunostomy. The reason why is not reported. Likewise it is not reported what the Foley catheter was manufactured from. This is important, as evidence suggest that the material used to manufacture the tube can cause differing rates of complications with the tube [633-635]. What is important to consider however, is that the choice of feeding jejunostomy is crucial and that it may be a major factor in the development of complications?

The insertion and type of the NCJ is not the only factor associated with the development of complications. The use of 'aggressive feeding' such as using high rates to initiate the enteral feed, coupled with the rapid increase in rate of the feed; along with the osmolarity of the feed are all important.

Delivery of Enteral Feed

Previous studies have demonstrated that the use of 'aggressive feeding' caused serious and even fatal complications in patients feed via a jejunostomy [509-511, 513-515]. The too rapid delivery of EN coupled with the overzealous use of opioids, which slow GI peristalsis, [369] could lead to increased intra-abdominal pressure and exacerbate GI oedema, reducing splanchnic blood flow increasing the likelihood of gastrointestinal ischaemia.

More studies are required to ascertain the nutritional requirements of surgical patients. It must be that differing requirements for nutrition are required at differing stages post-operatively. The equations by Elwyn (1980) [572] should be updated to reflect changes in surgical practices over recent decades.

The volume of EN delivered is vital. A study by Watters *et al* (1997) reported that EN delivered to nutritional requirements within 3 days in major surgical patients lead to respiratory problems secondary to increased abdominal distension. The maximum percentage of nutritional requirements achieved by the EEN group in the current study was 71.2% occurring on day 4 post-operatively.

The use of hyper-osmolar enteral feed has been reported as possibly contributory to both the intolerance of enteral feed and also the development of complications. Hyperosmolar feeds may cause a subsequent movement of both fluid and electrolytes into the GI lumen, leading to a possible increased intra-luminal pressure with its associated risks.

Feed aspiration is a potentially serious complication. No cases of aspiration were seen in the EEN group. The volume of NG aspirates was similar for both the enteral and standard group. It therefore seems logical that the slow and incremental delivery of enteral nutrition as used in the current RCT may have helped to prevent the accumulation of fluid in the stomach decreasing the risk of aspiration from occurring.

Gastrointestinal Function

Clinicians often assume GIT function by the detection of bowel sounds, the passage of flatus, and whether a patient has passed stools. The auscultation of bowel sounds is a rather crude method. Much work has focused on correlating bowel sounds with small bowel motility [404-414, 636]. To date there is still little consensus that bowels sounds actual reflect GIT motility.

Studies as detailed in section 1.5.1.5 illustrate that small intestine motility is evident 6-8 hours after surgical manipulation [384], however, this is not considered in clinical practice. Therefore, the qualification of GIT motility would undoubtedly prevent patients suffering from prolonged 'nil by mouth'. There are few non-invasive techniques available to quantify gastrointestinal motility.

The use of ultrasound imaging for the quantification of GIT motility has not reportedly been used in clinical or research practice. By using USS imaging in a sub section of patients in this RCT, it is apparent that EEN stimulates GIT activity. The EEN group had more peristaltic waves per minute on day 4, day 5 and day 6 post-operatively compared to the STD group. The difference between the groups reached statistical significance on days 4 and 5. This is a very exciting development and will be the subject of further investigation.

This study has shown that the use of EEN as compared to STD management stimulates GIT motility, which is also illustrated by a faster transit time and passage of flatus and stool in the EEN group. Several studies [12] [68, 415] have also concluded that EN stimulates the passage of stool and flatus, as compared to STD management. The mechanisms governing the increased GI motility in the EEN group are complex. The next section will detail the theoretical reasons as to why the EEN group had increased GIT motility.

Firstly, the delivery of nutrients (via the EN), directly elicit a fed state motility response [418], characterised by propulsive segmental peristaltic movements (section 1.5.1.5).

Secondly, the increased small intestinal motility in the EEN group may have been secondary to the improved distribution of fluid in the EEN, indicated by the fewer cases of oedema discussed previously. Research has shown that a positive fluid balance and presence of oedema negatively affect GI motility [570].

Thirdly, Mythen (2005) [383] concluded that PGID occurs in 90% of surgical patients. PGID is characterised by the inhibition of propulsive bowel motility. It is not however apparent from the paper by Mythen (2005) [383] what method of nutritional support was used, if at all. Likewise, if nutritional support was used, it is not clear whether it was enteral or parenteral nutrition. This is imperative as the use of differing types and routes of nutritional support affect the GIT in differing ways.

As discussed in section 1.5.1.5 the pathogenesis of PGID stems from the activation of a cytokine cascade by the surgical injury. The cytokines activate the enteric nervous system and the autonomic nervous system to alter GI motility, reducing GI transit time [384, 393, 394]. Coincidentally, the delivery of EEN dampens the GIT inflammatory response [46, 47, 473] as detailed in section 1.6.7. Therefore, the role of EEN in promoting GIT motility may be cytokine mediated.

Pain

Pain scores were comparable in both groups for the first 4 days post-operatively. However, on day 5 the enteral nutrition group had lower pain scores compared to the standard group ($t=2.655$ df 95; $p=0.009$). On day 6, the difference in pain scores was approaching significance ($t=3.970$ df 72; $p=0.053$). This difference may have been attributed to quicker resumption of bowel function in the enteral nutrition group.

Nausea and vomiting

Nausea and vomiting have been considered as symptoms of delayed gastrointestinal motility that occur post-operatively. Traditionally, in clinical

practice there is a view that patients who receive EEN have higher risk of nausea and vomiting. Several studies have refuted this concept [13, 14].

In this analysis, 15 patients (35.7%) in the standard group reported at least one episode of nausea in the 1st 7 post-operative days, compared to 15 patients (27.3%) in the enterally fed group (Chi=8.82; p=0.04). Vomiting in the first week occurred in 10 patients (23.8%) in the standard group and 8 patients (14.5%) in the enteral nutrition group (Chi=10.89; p=0.01). The incidence of nausea is higher than the incidence of vomiting. This is expected as nausea is subjective and often precedes vomiting.

The incidence of nausea and vomiting in the current RCT was higher when compared to a study by Biffi *et al* (2000) [64]. They reported that 1.25% of their patients developed nausea and vomiting. A similar cohort study reported that the incidence of nausea and vomiting was 15% [69]. These studies should be interpreted with caution. Nausea and vomiting is caused by many others factors such as inadequate gastric decompression, inappropriate use of antiemetics, analgesia and anesthetic are also contributory. It can be assumed that gastric decompression was similar for the two groups as similar volumes of nasogastric aspirates were recorded for the first 5 days. Likewise the use of analgesia and anesthetics are assumed to be similar in both arms of the current study as the same anesthetists are used for UGI resections.

It can be concluded that enteral nutrition does not accentuate nausea and vomiting as discussed in the previous literature.

Secondary Outcome 4: There were marked improvements in the nutritional status in Early Enteral Nutrition group post-operatively.

4.3.5 Improvement in Nutritional Status

As discussed in section 1.4, starvation and malnutrition lead to deleterious effects on physiological outcome. Keys *et al* (1950) [236] illustrated that depletion of body proteins will progress to impaired organ function.

This analysis suggests that the EEN group lost less weight, lost less muscle mass and function as compared to the STD group. This may well explain the marked reduction in the development of major complications seen in the EEN group. The next section will discuss the nutritional parameters in the context of the previous literature.

Weight Loss

All patients in this analysis lost weight post-operatively; the mean percentage weight loss was 4.2% from pre-operative stage to discharge. However, the EEN group lost less weight compared to the standard group (3% versus 6.2%) from pre-operative stage to when discharged from hospital. This was similar to the findings of the several studies [15, 16, 357, 358] [70, 291, 354-356] with the exception of the study by Watters *et al* (1997) [14] who refuted the fact that enteral nutrition post-operatively maintains the weight of post-operative patients.

These studies all had a calorie intake of 1138-1400 from the feed per day, which is comparable to calorie intakes, seen in the current RCT. Interestingly, none of these studies reported the incidence of oedema in the randomised groups. If weights were adjusted for the oedema, with dry weights reported the STD group might actually have lost more weight.

Feeding the Obese Surgical Patient

Forty-four percent of the sample was overweight or obese. This is similar to the series of UGI surgical patients reported by Ryan *et al* (2006) [70]. Obese patients

undergoing high risk surgery bring with them both technical difficulties for the surgeon as well as longer operating times, impairments in immune function, abnormal cardio respiratory function, metabolic derangements, abnormal homeostasis and higher incidence of post-operative complications [70].

Interestingly, obese patients tend to lose more weight peri-operatively. This is an interesting concept and really opposes the view held traditionally that obese patients can 'live off their excess fat' as a primary fuel after surgery and that in some way this is beneficial. Obese patients experience a block in both lipid metabolism and utilisation that causes them to use their lean tissues for the synthesis of glucose [637]. This predisposes an obese patient therefore to lose more lean body mass as compared to non-obese patients and therefore feeding is even more important in an obese or overweight surgical patient.

Muscle Mass and Function

Not surprisingly both groups had a reduced muscle mass and function post-operatively. However, the EEN group maintained more muscle mass (using MAMC) when compared to the STD group at discharge, 6 weeks and 12 weeks.

Similarly the EEN group maintained muscle strength (using HD) when compared to the STD group. The attenuation of muscle strength has been reported in several other studies [13, 14, 16, 361]. These studies used handdynonometry. One trial studied concluded that EN did not alter the strength of respiratory muscle function [14].

To date no published trials have studied both the loss of muscle mass using MAMC and function using HD to date. The theory being that the loss of muscle mass from peripheral muscle as indicated in this RCT may reflect loss of other types of muscle namely cardiac and other organ muscle. However this is merely hypothetical and would require further research to substantiate this theory.

The mechanism as to why the EEN lost less muscle mass and function, may pivot on the previously discussed theory, that EEN leads to increased production of insulin. Insulin is an anabolic hormone. It is antagonistic of the stress response, thus leading to possible attenuation of the stress response.

Resumption of oral Intake

This study has clearly indicated that the EEN group had an increased oral intake post-operatively. By day 7 post-operatively, 19% (8/42) of the STD group and 16.6% of the EEN group (9/54) had resumed oral intake. The whole EEN group appeared to progress to oral intake quicker than the STD group, with 60% of the EEN group and 22% of the STD group having oral diet by day 12. This is similar to findings from five studies [12, 16, 357, 360, 361] that have reported that EN as compared to standard management improved oral intake post-operatively.

As expected, the corresponding mean calorie intakes were higher in the EEN group throughout the study duration. However, both groups had an inadequate oral intake on day of discharge (1227 calories/day for the EEN group versus 812 calories/day for the STD group). The reason for reduced calorie intake is unclear. Presumably, lack of confidence with resuming oral intake after surgical resection and apathy could be responsible.

Appetite was reduced in 62% of the total study population on discharge, with 50% of the enteral nutrition group and 23.2% of the standard management only reporting good appetite on day of discharge. This corresponded with post discharge oral intakes remaining inadequate in both groups with 83% (N=35) standard group and 30% (N=16) enteral group eating less than 1000 calories per day.

This is similar to reports in another study, Ryan *et al* (2006) [70]. They reported that 60% of their patient's undergoing UGI resection had suboptimal food intake on and following discharge.

There are several suggestions why this RCT has demonstrated an increased oral intake and appetite in the EEN group:

1. The possible attenuation of the Acute Phase Protein Response as illustrate by improved nitrogen balance in the EEN group. However, as discussed this is not supported by the visceral protein and CRP.

2. Jejunal feeding bypasses the stomach and therefore does not cause satiation.

3. Reduction in complications and infections seen in the EEN group, increased appetite quicker than the STD group.

Number of Patients requiring Home Enteral Nutrition

On the day of discharge, 6 patients (14.2%) in the STD group required EN and were subsequently discharged home on EN. In comparison, only 1 patient (1.8%) of the EEN group was discharged home on enteral feeding. The main determinant of the need for home enteral feeding (HEF) was nil by mouth secondary to anastomotic dehiscence. The reported incidence of HEF in this study corresponded with the findings of the audit by Ryan *et al* (2006) [70]. They reported that 14% of their patients required HEF via a NCJ. The authors commented that the use of HEF was essential to maintain optimal nutritional status post discharge. The series by Ryan *et al* (2006) [70] stated that as 60% of their patients had suboptimal oral intake on discharge then the use of jejunostomy feeding should be much higher. To date the evidence to suggest that the use of HEF in patients post discharge is clinically effective is limited. It would seem logical that if a patient is nil by mouth then the use of HEF allows the patient to be discharged home, as continuing to keep a patient who is nil by mouth because of a complication without adequate nutritional support is clearly unethical. The issue however of routine HEF for patients who are anorexic and unable to achieve adequate nutritional intake orally requires further study. In the current study one patient was discharged home on HEF as a supplement to oral intake.

To date, no other RCTs have reported the need for home enteral nutrition post discharge in patients undergoing major UGI resection for cancer.

Secondary Outcome 5: There were no statistically significant differences between the two groups for Health Related Quality of Life; however there was a trend to an improvement in the Enteral Nutrition group.

4.3.6 Health Related Quality of Life

Measurement of HRQoL was considered to be an important secondary outcome for this RCT. HRQoL is a reflection of how a patient perceives his or her own health [579-589]. The personal burden of illness cannot be fully described by objective measurements of disease status alone. Studying HRQoL involves gaining information on several factors that influence well-being.

To date, the body of evidence suggesting that post-operative EN in surgical patients impacts on HRQoL is limited. To our knowledge this is so far the largest series of patients to compare HRQoL in patients who received either EEN or STD management in patients undergoing major UGI resection for cancer.

The SF-36 was used for a comparison of HRQoL. This questionnaire was chosen as it has been intensively used in previous studies and has been found to have high validity and reliability [590, 591]. The SF-36 asks about general health and offers response options (1=excellent to 5= poor).

Baseline Assessment of Health Related Quality of Life

The response rate for the baseline assessment of HRQoL was 81%. The reasons for not responding were not recorded. It is not unreasonable to assume that patients may not have completed their questionnaires for several reasons, including feeling anxious prior to surgery, feeling unwell or feeling overburdened. Not having access to the reasons for non-responding can affect the representation of the data set. Therefore once again it is important to state this in the reporting of this data in future publications, once again allowing the reader to make their own inferences on the validity of the outcomes

For this early analysis, the groups were comparable at baseline for seven of the eight HRQoL factors pre-operatively. However, the scores for social function were not comparable. The mean score was higher in the enteral nutrition group as compared to the standard group (t=-2.15; p=0.035).

The difference between the two groups for social function may have occurred by chance, as the other baseline HRQoL factor scores were similar. However, this could alternatively be an important finding, as it could be argued that the higher baseline score for social function in the EEN group may have contributed to the difference between the two groups for the primary outcome. A study by Blazeby *et al* (2005) [627] concluded that pre-treatment social function in particular was significantly associated with length of hospital stay (p=0021). The authors suggested from their studies that a reduction in social function by 10 points (using the EORTC questionnaire) corresponded to an increase in length of hospital stay by 0.93 days. The difference in scores for social function for the current study was 63.3 (SD 29.4) in the EEN group compared to 48.3 (SD 34.4)) in the STD group (t=-2.15; p=0.035). Therefore the difference between the two groups is 15 points. This difference could correspond with a LOHS of 1.4 days, if the results of the study by Blazeby *et al* (2005) [627] are conveyed to the current RCT. However, it is important to note that the two studies are using different HRQoL questionnaires.

Nevertheless, baseline quality of life scores for the different factors have been demonstrated to be independently prognostic of clinical outcome [627]. It is therefore important that the data is presented and the reader is able to make inferences regarding the impact on the primary outcome.

Post-Operative Assessment of Health Related Quality of Life

Post interventional analysis of the health related quality of life scores concluded that overall, UGI resection for malignancy has a negative impact on HRQoL as indicated using the SF36. The mean values for both groups, for all factors deteriorated post-operatively. This should be taken into account during patient selection for UGI resection, as the results of the HRQoL scores for the current

study suggest that HRQoL takes longer than 12 weeks to return to pre-operative scores.

Comparisons of the randomised groups indicate that there were no differences for seven of the eight factors. The only statistically significant difference between the two groups was for bodily pain. The EEN group had less bodily pain at 6 weeks and 12 weeks post discharge when compared to the STD group. This is an interesting finding. Possible reasons for this could be that the EEN group had less pain as a result of improved wound healing and hence less scarring. Better absorption of oral analgesia may be a possibility. Alternatively, it could be related to the APR, but typically this should have returned to a pre-operative state by 6 weeks post-operatively. Whatever the reason, this is an interesting finding and requires further investigation.

The SF-36 is a general health status questionnaire. It may be that it was not specific for patients with a diagnosis of cancer. Other disease specific questionnaires may have reported a difference in HRQoL. This may be the reason why the EEN group did not show more of an improvement in HRQoL as it is not unreasonable to assume that any intervention that reduced LOHS, reduced the development of major complications, and was generally well tolerated by the patients who received it, should have had a more positive impact on a patient's HRQoL.

Frames of Reference

Fayers and Sprangers (2002) [638] illustrated that the response given to HRQoL questions is dependent on what the patient has in mind when they are due to respond. For example, " What is your overall quality of life during the past week?" This seems a simple question, but the response is very much dependent on what the patient is comparing it to. The authors [638] suggested that patients may employ differing frames of reference, which result from responses that are derived from implicit comparisons with various peers groups or with themselves before they were ill. The patient may respond, "Compared to others (in hospital or in clinic) who are very ill I am doing very well". Thus, it could be argued that if a patient is in clinic or just admitted for surgery and sees others around, they

may well think they have a reasonably HRQoL. A study Fayers *et al* (2007) [639] concluded that patients varied in the comparisons they used when completing HRQoL questionnaires. The results showed that 1/4 of patients compared themselves to before they were ill; 1/4 compared themselves to healthy peers; 1/3 compared themselves to I year ago. The authors reported that these proportions were similar at all time points for data collection. As expected these respondents had markedly different HRQoL scores. This is termed reference frame utilisation.

In many RCTs it may be expected that the reference frame utilisation will be randomly balanced across the study arms. The main consequence of this will be loss of efficiency because of extra variability that has been introduced.

For this RCT it may have been useful to ask the patients what they were basing their comparison on when they report for their HRQoL, in an attempt to try to understand the variations in responses for the two arms of the study. Investigators have used questions such as " compared to others of your age" and used this a basis for completion of HRQoL questions [640]. Any future studies conducting should attempt to standardise the basis of patients when they are answering HRQoL questions.

Re-Calibration

Recalibration of individuals following a diagnosis of cancer may also be a reason why they were no differences reported between the two groups in terms of HRQOL. Re-calibration suggests that patients redefine for themselves what is important to them [641].

It may be that following a diagnosis of a potentially life threatening disease and the knowledge that a major surgical resection is required may produce an individual to reprioritize what is important to them. Therefore they may well present their HRQoL in a more positive way then they may have previously. A respondents' response may be dependent of life experiences and contact with other people [641].

Location of Patient

Criticisms could be made of studies if the patients in each randomisation group attend different clinics. This could be stated for a study that compared surgical intervention for UGI cancers with oncological treatments. These differing healthcare treatments would be delivered in differing clinical settings and would have implication for the results of HRQoL questionnaires. This was not the case in the current RCT as all patients were treated in similar clinical surroundings and attended the same clinics.

Contact with Research Team

It may be suggested that any improvement in HRQoL in an RCT in the interventional arm may reflect bias; attributed to the increased patient contact between a member of the research team and the patient. However, it is assumed that each group had the same number of follow up appointments and there were no additional visits or time spent with either the STD group or EEN group.

Positive Response to Treatment Intervention

Another source of bias could be the awareness of the patient that the research team expected a positive response from the enteral nutrition and hence patients may have produced a more favourable response. Similarly, 'resentful demoralisation' may have occurred in the control group. As there were no statistically significant differences between the two groups for 7 out of the 8 factors it is unlikely that these biases were an issue of concern in this RCT.

Secondary Outcome 6: Early enteral nutrition provided a potential cost saving of £1,241.06 (£828.36-£5,315.40) per patient if delivered within 12 hours of leaving the operating theatre as compared to a patient who received standard post-operative management.

4.3.7 Cost Benefit

Very few RCTs have been designed to compare the financial costs of using EEN versus standard hospital management post-operatively. The results of this RCT are in line with findings of a study in USA by Hedberg *et al* (1999) [530]. This study [530] concluded that EEN delivered via a needle catheter jejunostomy feeding tube within 12 hours of major surgery as compared to standard care led to a cost saving of $4,450 per patient in the early EN group in patients post major GIT resection. Other studies [12, 13] have surmised that delivering enteral nutrition lead to a 50% cost saving as compared to the use of STD management. These results are once again in line with the findings of this RCT.

Moreover, using EEN avoids the need to use TPN with its attendant risk and expense [40, 642]. In addition to providing a safe effective route for enteral nutrition and avoids the need for parenteral preparations and intravenous drugs reducing real costs in terms of nursing time and drug costs.

For simplicity, the current RCT calculated the costs of the differing LOHS and the costs of treating the significantly different major complications of the two-randomised groups. The rationale for this was that these two costs were the main differential cost drivers. In an ideal world, this study would have performed a rigorous cost analysis, taking into account absolute costs. This would have meant more sophisticated data collection of exact drugs (including dosages and frequency of administration), ward stay and level of dependency of care, exact costing of theatre time and care, and allied healthcare profession input. This was deemed outside the remit of this thesis and RCT. Coupled with this, today's bed pressures with critical care beds, the actual location of a patient does not clearly reflect the level of dependency of that patient and the nature of the treatment that patients should be receiving.

4.4 Methodological Issues of the Study

A research trial should have the aim of answering a specific question, however, practical constraints will limit the trials conduct. This next section will discuss the methodological issues and potential limitations of the current RCT.

4.4.1 Trial Design

"The RCT is a very beautiful technique of wide applicability, but as with everything else there are snags. When humans have to make observations there is always the possibility of bias"

CONSORT STATEMENT [560]

Sample size/Early Analysis

The sample size of this early analysis was 102 patients. It was intended to recruit 160 patients but due to slower than anticipated accrual, it was necessary to perform an early analysis of the dataset to meet the submission deadline of the University for completion of the thesis.

Recruitment did, however, continue after the early analysis for this thesis, as funding was available, and the investigator was concerned that one of the main criticisms of previous studies has been inadequate sample size to yield adequate statistical power (i.e., 80% power), leading to Type II error. However, performing an unplanned early analysis of the dataset has several limitations [560,601]. These include:

1. An interim analysis should be planned and outlined in the initial trial protocol. The main reason for performing an interim analysis is usually for patient safety, but sometimes the analysis is used to check the potential of the study to be adequately powered to establish efficacy. The early analysis of the current RCT was not planned but was conducted for pragmatic reasons regarding the need to meet submission deadlines; the use of term 'interim analysis' was felt to be misleading.

2. The analysis for this thesis therefore deviated from the scheduled analysis in the original protocol: consequently, there is a potential to weaken the confidence of the inferences drawn by from the RCT. The results of this analysis should be interpreted with caution, as there is a risk of the treatment effect being overestimated.

3. The results of an interim analysis should be kept confidential. This is to maintain clinical equipoise amongst the trial and clinical team. The PI and independent statistician (supervisor) were the only individuals to see the results of the early analysis before the data collection for the main study was finalised. The results of the early analysis were therefore not cascaded to the surgeons or clinicians involved in the trial: subsequent presentations to this group were based on the results of the fully completed trial only.

   The MRC now recommends the appointment of a Data Monitoring and Ethics Committee (DMEC) as a way of limiting potential bias within the data management and analysis of a trial, particularly for large scale, multi-centre trials. A DMEC would normally be composed of experts in the field who are external to the Sponsoring organisation: the main task for such a group is to supervise decisions about interim analysis and establish the stopping rules for a study based on safety or efficacy issues. A Data Monitoring Committee was not established for the current trial as this was perceived to be a small-scale clinical trial based in a single region when the protocol was first developed: however, in line with more recent developments in the quality assurance of trials, the establishment of a DMEC is recommended for future studies.

Stratification and Randomisation

Stratification for this RCT was by hospital centre. This is typical as multicentred RCTs often have separate randomisation blocks for each centre to limit the differing ward-based procedures in each centre affecting the trials' outcome.

As discussed in section 2.2, the goal of randomisation is to prevent bias. To be truly effective the design and conduct of the clinical trial should ensure that the investigator, the clinical team and the patient are unaware of the treatment group to which the next patient is assigned. If this can be predicted, bias is introduced.

Many trials of nutritional support have not described their allocation sequence or randomisation technique. Therefore judgments cannot be made regarding the quality of the trial. These trials should be interpreted with caution.

The current RCT used block-stratified randomisation. The reasons for this are presented in section 2.2.3.1. Critics may argue that the process for randomisation in this RCT was not sufficiently robust. The use of blocks of 30 was decided after discussion with a statistician. In hindsight maybe smaller blocks would have been more appropriate. This would have possibly prevented the imbalance in the two groups. Concurrently, the use of remote telephone randomisation services may have been the optimum. Due to the relatively small-scale nature of the current RCT this was not considered practical or financially viable. Any future studies would use the resources now available for remote telephone randomisation as a result of the establishment of the Welsh Cancer Trials Unit [603]. This facility was not available at the time when this RCT was being developed.

Blinding and Placebo

Whilst developing this RCT, the feasibility of blinding and using a placebo were considered in the development of this RCT. Blinding would have involved the patients receiving placebo via an enteral feeding system, which would have needed to be specially manufactured to be opaque. Usually, the enteral feeding systems are transparent so ward staff and investigation team would see if enteral feed solution were passing through it. To commission specially manufactured feeding systems, would have been costly, and impractical for this trial.

In conjunction, the effect of the placebo itself could bring forth its own physiological affect, giving false results not typically associated with STD management. One study [12] used a placebo of saline versus enteral feeding.

The placebo group had a high complication rate, which might have been associated with the lack of enteral feed or the use of saline.

Also the effect of using water as a placebo could have more serious complications. A study by Schloerb *et al* (2004) [516] from a series of patients who had jejunostomy inserted, and received water only, concluded that water may have predisposed the patients to a high risk of small bowel necrosis.

These reasons alone, suggest that the use of placebo requires careful consideration and for the current RCT, it was not considered beneficial or useful to use placebo. It was believed that by using a placebo, confusion would have occurred, as the aim of the hypothesis, was to compare STD management with EEN. Fundamentally, pragmatic clinical trials aim to mimic clinical practice, and rarely use blinding or placebos.

Patient selection

The sample of patients included in the current RCT had UGI cancer. This trial sample is considered to be homogenous. The meta-analysis by Lewis *et al* 2001)[17] compared patients with all types of GI conditions, colorectal and UGI, including both benign and malignant disease.

Initially, the pilot RCT originally set out to recruit all GI patients. It became apparent that the consent rate for the colorectal patients was reduced.

The poor consent rate was probably attributed to the need for the colorectal patients to receive their EN via a nasoenteral feeding tube, placed prior to surgery. The use of nasojejunal tubes rather than NCJ was considered preferential in the colorectal group, as the duration of nil by mouth in colorectal patients tends to be shorter than UGI surgical patients. It was therefore considered inappropriate to insert a percutaneous tube. The tubes were also inserted prior to surgery to allow migration of the tube into the small bowel with normal peristalsis present pre-operatively. Compliance with this procedure was poor as shown another study by Lia *et al* (2003)[643].

Over recent years, the Enhanced Recovery after Surgery programme (ERAS) [529] suggested that patients having major colorectal surgery can be orally fed immediately post-operative, therefore the routine use of enteral tube feeding is no longer necessarily relevant.

Small amounts of demographic and surgical data were collected on the patients who did not consent to the RCT. This was to ensure that the study sample was not markedly different from the patients who did not consent. As presented in table 2.4.3 the baseline characteristics for the study sample and the non-consenters were not different. There were no statistical differences for age, gender and type of tumour between the randomised patients and the patients who declined consent. More patients, however, in the RCT had tumours that were stage III and IV compared to the patients who declined consent. Therefore, it could be said that the trial consisted of patients with more advanced disease. Many RCTs have not collected data on patients who decline consent. Therefore, it is hard to make any assumptions on the generalisability of the findings.

4.4.2 The Treatment Regimens

Standard management

The STD management used in this RCT was defined as nil by mouth until the operating surgeon deemed the patients safe to tolerate oral diet and fluids. This was typically 7-10 days post-operatively. Whilst, this is based on routine post-operative management, it is still ambiguous. Some surgeons allow their patients to drink sooner than others, but this was not considered problematic as patients often had a gastric decompression tube. Thus, the contribution of this fluid to actual nutrient intake was considered to be negligible.

As the trial evolved, the gastrectomy patients tended to commence oral fluids at 5 days, once again dependent on the surgeon preference.

These variations in clinical practice only reflect the complexity involved with conducting clinical trials of this nature. Once again, if meticulous randomisation procedures have been used, these variations do not alter the trial's findings.

Early Enteral Nutrition

The current RCT used enteral nutrition delivered in to the jejunum. There is much confusion in the literature with many authors reporting simply the use of enteral nutrition. They have either not considered, or have considered but not appreciated, that differing modes, routes and types of enteral nutrition have potentially differing effects on clinical outcome. The timing of commencing enteral nutrition, the amounts of enteral nutrition delivered and for how long, are all relevant and need to be reported in detail.

Two studies, did however stress the importance of reporting the time of commencing, the route, the type, the duration and volume of enteral nutrition in clinical nutrition trials [447, 644].

Time of Commencement of Enteral Nutrition

It is apparent that there is variation as to when the nutritional support is commenced post-operatively, with some commencing EN immediately after the patient returns from the operating theatre [12] [13], some starting within 24 hours [503, 521] [16], and some commencing within 24-48 hours [357]. One study commenced EN after 3 days [358]. The delay in starting the EN is relevant.

A study [538], concluded that for EN to be beneficial it needs to be both early (within 12 hours) and delivered in sufficient amounts. The authors concluded this might be the reason why many trials do not show any benefit with early enteral nutrition. The time when enteral nutrition was commenced for this RCT was standardised. Enteral nutrition was routinely commenced between 6pm and 8 am after the patients returned from the operating theatre.

Feeding Regimen

For this trial, the feed rate commenced at a low rate and incremented slowly. The mean feed volume never exceeding 80mls/hour and 75% of nutritional requirements as calculated using the Elwyn equation [572].

The results of the current RCT indicate that delivering feeds to achieve nutritional requirements may not be necessary and that lower rates of feed may be sufficient.

However, similar outcomes as seen in the current RCT, may be achieved with a lower volume of EN. Similarly, a better outcome may have been achieved with a higher volume of feed. Only by exploring the technicalities of delivering the EN in future studies will this be concluded.

Clinical staff need to be educated on the optimal method of enteral feeding. This education needs to emphasise the importance of:

1. Enteral nutrition should be commenced early, i.e. within 12 hours of the surgical procedure or sooner, if practical.

2. The initial rate of commencing the enteral nutrition needs to be low i.e. 10-20 mls/hour.

3. The enteral feed rate should be increased slowly i.e. 10 mls/hour every 12 hours as delivered in this RCT.

4. Enteral nutrition does not need to be delivered to achieve nutritional requirements. The current RCT did not deliver EN higher than 70% of calculated nutritional requirements [572].

5. The insertion of the jejunostomy requires a skilled surgeon with meticulous technique.

Type of Enteral Feed

There are many types of EN available on the commercial markets. These can be categorised into whole protein, semi-elemental (pre-digested), elemental, disease specific and immuno-nutrition feeds. It is not evident in several studies

the type of feed that was used. The current CT used a whole-protein commercially prepared enteral feed for oesophageal and gastric patients, and a pre-digested semi-elemental enteral feed for pancreatic patients. Different brands were used in each centre, depending on that hospital centres enteral feed contract. All brands had comparable nutrient composition and were equivalent.

Duration of nutritional support given

The patients in the EEN group received EN for an average of 14 days. The EN was delivered until the patient was eating ¾ of their calculated nutritional requirements. As a result there was variation in the duration of time the EEN group received the EN. This was not considered problematic and just reaffirmed the need to study these patients in a pragmatic approach, as variations are inevitable.

4.4.3 Complication Rates of the Sample

Most surgical procedures are aimed at reducing patient suffering and improving functionality. Therefore, the development of a surgical complication is an unexpected and unfavourable result. Complications are considered as an important reflection of quality of care [645].

The validity of reporting of surgical complications is dependent on two issues. These are the definitions used and the validity of the recording systems. These will be discussed in the following section.

Over recent years, surgical morbidity has been categorised into major and minor complications, but crucially ambiguity remains as to how these are defined [579]. Rampersaud *et al* (2006) [646] stated that 'presently there is no clear consensus on definition of complication in the surgical literature'.

As presented in section 2.1.6.2 (table 2.2.1), the current RCT had clear definitions for complications. These were based on definitions used in a previous enteral feeding study [338].

In 2004, Dindo *et al* (2004) [647] published a classification system for surgical complications. Complications were classified into five categories depending on the intensity of the treatment required for the complication. Future surgical clinical trials should aim to use such a classification system, in an attempt to standardise the repoting of complications. This will improve the comparison of the incidence of complication rates across institutions. This is considered a common problem in surgical research at present [647] [645, 646].

The reporting of complications in clinical trials can therefore be criticised. It is for these reasons that the incidence of major complications was not chosen as a primary outcome, unlike many other clinical nutrition trials [12, 14, 503].

The current RCT used a prospective data collection for recording of the surgical complications. This ensured they were recorded as they developed, ensuring all complications were recorded, which was considered essential to gain an accurate incidence of all complications. The use of retrospective data collection for monitoring complications is dependent on stringent documentation in medical and nursing records, and reliable and accurate use of terminology by clinical staff.

The acceptable complication rate for UGI surgery is approximately 20%; with 60% of patients reported to develop minor complications [30, 579]. The overall major complications rate for UGI surgery should not exceed 20% [19].

The total number of major complications developed in this RCT by the sample population was 95. This equates to nearly every patient in the RCT developing a major complication, on average. The current RCT reported the total number of major complications developed. Several patients developed more than one complication. Therefore the sample for the current RCT appear to have

developed more major complications than reported elsewhere in the literature [19, 579]. There are several reasons to explain this.

1. Firstly, did the authors of previous studies equate the development of multiple complications by a patient to one complication or several complications? This will clearly affect the complication rate reported.

2. Secondly was stringent reporting of complications used in clinical trials? This is dependent on both the definition of the complication used, and the frequency monitoring by the trial team.

4.4.4 Concordance

Patient concordance is often a problem for researchers. An adequately powered trial can be planned, but if a large proportion of the patients in the treatment group fail to tolerate it, the results will be affected. A number of investigators have further divided patients into compliant and non-compliant for the final analysis [648-650], while others have simply withdrawn those who fail to comply [539].

Patient concordance was not a significant problem in the present RCT, as the EN was delivered via a NCJ and was generally well tolerated (section 3.6.5). The main issue of protocol compliance was from clinical staff.

Eight patients in the standard group (19%) were commenced on enteral feeds prior to 7 days post-operatively, in the current RCT. This was because clinical staff had a belief that this was beneficial for the patient. Concomitantly, 9 patients (16%) in the EEN group had their enteral feed stopped in the first post-operative week. The reasons are presented in table 3.25.

Of the 9 patients who commenced on EN, 5 of the patients had a suspected chest infection. As evident from the LOHS of these patients, none of these patients had a particularly complicated hospital stay. The clinical practice of stopping the EEN was based on the surgical teams assuming that stopping the EEN would benefit the patient. As discussed throughout this thesis, the crucial and reportedly optimal time for the delivery of the EN is when the patient is

stressed and hypermetabolic, as occurs in the present of an infection. Had the patients subsequently developed a chest infection, this may not have been optimal treatment for the patient.

One of the patients had their EEN stopped because of developing a chylothorax. This patient consequently was commenced on TPN. Evidence supports the continued use of EN in patients who developed chylothorax, however, the knowledge of this option being available may not be widespread amongst surgical staff.

The patients who 'switched' groups were analysed on an intention to treat basis. Whilst this is a limitation of this RCT it serves to highlight the actual benefits of EN, as the STD group probably benefited from the use of EN.

Concordance is always going to be an issue in clinical trials. An alternative view is that poor compliance represents the true situation in real clinical practice, and therefore is not a major methodological problem. If good compliance cannot be achieved in a research trial, where patients are usually more closely monitored, it is unlikely to happen in routine practice. This means the results are applicable to the real situation in hospital.

4.4.5 Health Related Quality of Life

As presented in the methods section the SF-36 health related quality of life questionnaire was given to all patients pre-operatively, on discharge, at follow up at 6 weeks, 12 weeks, 6 months and 12 months. The score for social function was statistically significant at baseline between the two-randomisation groups. Any future analysis should adjust for this difference at baseline to determine the impact (if any) on the primary outcome. This could be conducted using sensitivity analysis.

4.5 Generalisability

4.5.1 The Clinician as Principal Investigator

Some critics may have concerns about the principal investigator being a dietitian with a natural enthusiasm for the 'new treatment' i.e. early enteral nutrition may have affected the judgment of patients. This notion would be a particular issue if subjective outcome markers were used, but as the current RCT had a robust, objective primary outcome, which was clearly defined, this was unlikely to be a limitation in the current RCT. In addition, multiple safeguards were put in place to prevent this from occurring as discussed in the data management section (2.3.).

4.5.2 Generalisability of findings

The generalisability of a trial describes how the outcomes of a research trial can be used in other healthcare organisations or settings. Generalisability cannot be assumed, however. A RCTs' capacity to promote change in clinical practice and healthcare policy centres on how closely the trial's sample resembles the general population of patients with the same diagnosis that has been investigated. The CONSORT criteria provide a framework for empirically assessing and reporting generalisability. There are two main issues, these are

1. Is the patient population representative of the broad target group?

2. Can the results be generalised to an individual or group that differ from those in the study, with regard to age, sex, severity of condition or disease and co-morbid conditions.

Is the treatment package acceptable?.

Representation of Patient population

The main advantage of pragmatic trials over explanatory trials is that they increase external validity or generalisability of the findings; this is because the conditions that the trial was conducted to mimic the actual clinical surroundings and healthcare settings where the intervention is typically delivered. The current

RCT used minimal eligibility criteria, as typical in pragmatic clinical trials. This ensures that the study population is diverse, with numerous confounding factors.

Providing a detailed outline of the baseline characteristics of both the study population and the randomised groups, allows the readers to decide whether the sample population resembles the general patient population with the condition. The current RCT baseline characteristics are presented in section 2.4.3. Similarly, presenting data on patients who were and were not enrolled in the trial is important, as presented in table 2.4.2.2. If the two populations are similar, the generalisability of the trial is increased. The current RCT participants are assumed to be reflective of most patients undergoing major UGI resectional surgery for cancer.

Generalisability of Treatment Packages

The generalisability of a treatment packages is crucial. There are three factors that determine this; feasibility, acceptability and effectiveness. These will be discussed next.

Feasibility

Feasibility is essential. Providers of healthcare will only implement a feasible intervention. The results of the current RCT conclude that EEN is feasible via a NCJ as detailed in section 2.4.6.4.

Feasibility will however vary across differing organisations. The presence of local "champions" have an influence. These "champions" must educate others regarding the crucial factors needed to make the intervention feasible. Failure to deliver on one of these factors could affect the efficacy of the intervention. Feasibility also has a cost dimension; an unaffordable intervention lacks feasibility, being cost ineffective. The costs associated with the delivery of the actual enteral feed are relatively small (table 3.51).

Acceptability

An intervention must be acceptable before its use becomes routine in clinical practice. The current trial did not ask patients about their satisfaction with the EEN or the STD management.

Acceptability amongst the multidisciplinary (MDT) members is also crucial. A positive view of the treatment promotes its use. For the current RCT, some MDT members did have a negative attitude to the use of EEN, however this subsided as the trial continued. Once again, education and training are vital to ensure clinical staff have confidence in the results of the research.

Effectiveness

For an intervention to be effective the recipients of that treatment must have capacity to benefit from the intervention. Conducting high quality RCTs comparing two differing treatment will provide the evidence that an intervention is effective. More high quality RCTs are needed in the field of nutritional support, to determine its effectiveness in other specialties.

4.6 General Interpretation of the Results

This early analysis of an ongoing multi-centred RCT of 96 patients indicated that the use of EEN in post-operative patients maybe beneficial when compared to STD management i.e. nil by mouth, in reducing LOHS which was the primary outcome indicator. Whilst LOHS has limitations, it does give an insight into improvements in clinical outcome. It is the 'yard stick' by which hospital managers and commissioners of healthcare services substantiate the complexity and severity of surgical procedures.

The EEN group developed three times fewer major complications than the STD group. Despite the multifactorial origin of complications, which include issues with the actual surgical technique, the anaesthetic, or the postoperative management such as fluid balance and analgesia prescription, these confounding factors should be evenly distributed with meticulous randomisation.

The baseline groups were equivalent for many confounding factors as detailed in the discussion. However, the difference in the baseline scores for social function needs to be considered when interpreting the results of this analysis.

4.7 The Implications and Implementation of Findings

One of the main criticisms of clinical research is the difficulty of incorporating the findings into clinical practice. The successful dissemination of results is essential if current clinical practices are to change. The introduction of Clinical Governance [615] should help to assist in the implementation of the RCT results. Clinical governance is:

"The system through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care, by creating an environment in which clinical excellence will flourish".

Any intervention that reduces LOHS is useful. The employment of clinical dietitians are needed to ensure the safe and feasible delivery of EN to yield the results demonstrated in the current RCT. Unfortunately the number of funded dietitians currently working in surgical units, is limited, across the UK. Allocation of funding and subsequent recruitment of dietitians is imperative. Convincing hospital managers of the benefits of allocating funds for dietitians is central to the success of implementation of these results. The reinvestment of any potentially released monies, resulting from the reduced LOHS and major complications, seems sagacious.

4.8 Summary and Recommendations for Future Work

This thesis set out to compare the effects of EEN versus STD post-operative management in patients undergoing major UGI resection for cancer. The conclusions from this early analysis imply that patients do benefit from the use of EEN post-operatively and this yields a cost saving for healthcare organisations.

Whist conducting and analysing the results and debating these in the discussion several questions have arisen which require further investigation. These will be detailed in the next section.

1. In the current RCT EEN was commenced within 12-24 hours of leaving the operating theatre. Future studies could explore whether initiating nutritional support pre-operatively and continuing the EEN through the surgical resection can intensify the effect of EEN. Evidence from studies [427-431] suggest that GIT mucosal integrity is altered after initiation of an APR. Cummins *et al* (1995) [439] concluded that EEN is less effective at maintaining GIT mucosal integrity after the initiation of an APR. The authors suggested that there was a crucial window i.e. within 12 hours of theatre that EEN is most beneficial. Future studies should explore whether EN commenced in the immediate pre-operative period is better than EEN commenced post-operatively.

2. The actual prescription and delivery of the EEN is essential. A previous study [14] has demonstrated that the use of 'aggressive feeding' can lead to complications with the jejunostomy tube and increases the incidence of distension and abdominal bloating. The current RCT commenced the EEN at 10-20 mls/hour and then subsequently slowly increased the EEN by 10mls/hour per day over the first 5 days post-operatively. Future work could explore whether the EEN actually needs to be increased in the first post-operative week above 20 ml/hours, whilst the patient is catabolic. The theory may centre on delivering sufficient EEN to prevent GIT mucosal atrophy; but not increasing EEN may prevent any increase in luminal pressure, which may cause GIT complications.

Likewise not increasing EEN above 20mls/hour may prevent hyperglycaemia that once again may further decrease complications.

3. This RCT has studied the delivery of EEN via a needle catheter jejunostomy inserted at open laparotomy at the time of the resectional surgery. Whilst this RCT reported no major or fatal complications attributed to the NCJ other studies have reported both major and fatal complications [358] [488] [500, 503, 505, 507, 527]. Future studies could compare the use of nasojejunal tubes or double lumen gastro-jejunal tubes to deliver the EEN so perforation of the small intestine was not necessary. One study reported that the use of Jejunostomy is considered a 'small bowel stress test' [500]. The theory may centre on the action of perforating the small intestinal luminal wall may deleteriously affect the immunological response initiated from the Peyers patches [46, 47].

4. The sample population of this RCT so far had a reduced oral intake (both protein and calories), prior to surgery. Previous studies have confirmed that post-operative recovery and hence length of hospital stay may be proportional to pre-operative nutritional intake. Future studies could aim to correlate whether oral intake has a negative affect on recovery and whether pre-operative enteral tube feeding is beneficial in improving post-operative recovery. Future studies should possibly stratify for pre-operative oral food intake. Likewise a retrospective study using correlations of pre-operative oral protein and calorie intake may provide some evidence.

5. This study has concluded that EEN is beneficial for patients with UGI cancer undergoing major resectional surgery. The beneficial effect of EEN (section 1.5) may centre on the optimisation of the immune response mediated by the Peyers Patches in the small intestine. It may be therefore that the use of EEN may benefit other groups of major surgical patients. Future studies should explore the use of EEN versus standard post-operative management in the following

cohorts of patients; gynaecology, cardiac, head and neck, thoracic, vascular and in paediatric surgery.

6. Hyperglycaemia is detrimental to post-operative outcome predisposing to increased risk of complications particularly infective complications [651]. A study in critical care patients [652] demonstrated that 'tight glucose control' using exogenous insulin improved clinical outcome. It would be useful to explore whether tight glucose control improves clinical outcome in post-operative patients having EEN. The use of exogenous insulin infusions for the first post-operative week compared to routine post-operative management to determine the effect on differences in major complications would be interesting.

7. Future studies should compare the use of post discharge enteral feeding compared to the use of oral diet alone. Ideally, the enteral nutrition should be continued throughout the post-operative phase and then patients could be re-randomised to either post discharge feeding or oral diet alone. This study has confirmed that the EEN group maintained their body weight as compared to the STD group. However following discharge the EEN lost more weight than the STD. This equated to 7.5 kilograms in the first 6 weeks and total 9.3 kilograms at 12 weeks post discharge. The reasons for this loss maybe secondary to reduced oral calorie intake up to 6 and 12 weeks post discharge. The mean oral calorie intake of the sample population was less than 1500 calories per day. What is not clear is why the EEN group had a higher calorie intake at each time point when compared to the STD but yet lost more weight. It may be that the EEN group had in someway adapted to need a higher calorie intake and once the enteral feed was discontinued, the weight loss was more extensive.

8. The current study has provided the evidence that EEN is superior to standard post-operative management in patients undergoing major UGI resection for cancer. This was conducted as a clinical trial. What is now important to determine is why EEN is beneficial. A study of cytokine response to both EEN

and STD management is essential however ethically this may not be possible in patients, as it may no longer be ethical to withhold a beneficial treatment to study the mechanism as to why it may be beneficial. As a result this study may need to be conducted in other types of patients and the results then extrapolated to the type of patients studied in the current RCT.

9. The fluid balance of a patient greatly impacts on their clinical outcome [255]. The current RCT has reported that the STD group developed more oedema compared to the EEN group. Future studies should aim to explore the reasons for this difference. Is the increased report of oedema in the STD group a result of the lack of nutrition delivered or is it a result of the increased quantity of intravenous fluids? This study did not report the types of IV fluids delivered in either randomisation group, this data will be analysed for future studies and publications.

Another possible reason for more patients in the STD group developing oedema could centre in the APPR. All these possible factors should be explored in further prospective studies in an attempt to answer this important question.

10. The study has demonstrated that the use of EEN stimulates GI peristalsis as compared to the use of STD management. Once again the mechanism for why this occurs is not answered by this clinical trial.

Further investigations are therefore required centering on the activation of proinflammotory cytokines, which have been postulated to be central in mechanism of altered GI peristalsis [390-392]. Intestinal surgery is thought to activate the macrophage network in the intestinal luminal wall setting up an inflammatory reaction. These macrophages express CD11A and 11b/CD18 and interleukins IL-1, IL-6 and TNF alpha. These act locally to initiate morphological changes in the bowel wall. In addition, these immunological cells cause an increase in free radical production, which disrupts the membrane ion-channels (potassium and calcium) that regulate smooth muscle contraction and rhythm. The result is a decrease in circular muscle contraction and thus a reduced intestinal transit time. Subsequently, systemic cytokines, prostaglandins and catecholamines are released which activate the autonomic nervous system. This

produces the inhibitory effects altered motility and reduces mesenteric blood flow. This was eloquently illustrated in an animal studies [393] [394] [384]. This should now be explored using USS imaging as detailed in the current RCT and correlating this with cytokine studies.

11. To date no RCT has studied the effect of using EEN and STD management on survival in cancer patients undergoing major resection. If EEN had an immunological response, it may be possible that it may affect survival. Future studies should aim to quantify any possible effect.

12. A study [627] demonstrated that pre-operative baseline factors of HRQoL correlate with both short-term outcome i.e. post-operative complications and length of and long term and survival. Future studies should aim to correlate baseline results of HRQoL from the current RCT and clinical outcome and survival.

13. Future work should focus attention on patients deemed palliative and therefore not eligible for curative intent resection. The benefit of enteral nutrition may well have considerable benefits on patients either undergoing palliative surgery or palliative chemotherapy or radiation therapy, having a potential impact on survival and HRQoL.

14. As discussed throughout this thesis, to date there has been no Cochrane systematic review of the use of peri-operative nutritional support. This should be conducted in the near future.

5. Conclusions

The provision of early enteral nutrition delivered via a needle catheter jejunostomy within 12-24 hours of leaving the operating theatre may improve clinical outcome by reducing length of hospital stay in patients undergoing major upper GI resection for cancer.

No differences were found between the EEN group and the STD group or HRQoL but patients in the EEN group did develop substantially less major complications in hospital. As a result there was an estimated cost saving in the region of £1800 per patient is EEN was used.

The results of this early analysis of an ongoing RCT have potentially important clinical connotations.

6. References

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Nutrition is considered so basic to life that to withhold it requires special and profound circumstances. By withholding medical treatments this may allow the disease process to progress; withholding nutrition can create a fertile ground for disease occurrence and progression"

Scott Berry and Joseph Lacy, 1996 [653]

Appendices

I. Appendices to supplement the Literature Review

I.I Gastrointestinal Motility

Gastric Motility

Regulation of gastric emptying is controlled by receptors in the duodenal and jejunal mucosal that detect changes in acidity, osmotic pressure and fat content.

Peptides, fatty acids and amino acids in the duodenum decrease the rate of gastric emptying. They also stimulate the production of cholecystokinin (CCK) and glucose insulinotropic peptide (GIP) hormone, both of which also decrease gastric emptying. Peptides in the duodenum and jejunum release gastrin from the mucosal lining in the stomach and duodenum. Gastrin acts to increase the contraction in the antrum and cause the pylorus to constrict further

In addition the presence of hypertonic solutions such as chyme in the small intestine, stimulates a feedback mechanism inhibiting gastric emptying. In addition the presence of acidity (pH <3.5) in the duodenum slows gastric emptying (some enteral feeds are acidic) the inhibition of gastric emptying in response to acids has both a neural and endocrine component. The hormone secretin is released from the central nervous system and GI plexus neurons along with CCK and GIP and gastrin to act as neurotransmitters and neuromodulators. They inhibit antral contraction directly, but also increase the production of pancreatic and liver bicarbonate which neutralise the pH of the acid gastric chyme in the duodenum allowing the quicker activation of pancreatic enzymes which function optimally at a neutral pH.

The above effects result in fat not being emptied into the small bowel at a rate greater than it can be emulsified by bile salts. In addition gastric acids are inhibited from being delivered into the duodenum too quickly so that the acidity can be neutralised by pancreatic and duodenum secretions.

Motility of the Small Intestine

The small bowel is the largest segment of gastrointestinal system. It is approximately five metres in length, and chyme (undigested food) normally takes 2-4 hours to pass through to the small intestine. The first 25 cm is the duodenum, which has no mesentery and is thus easily distinguishable from the rest of the small intestines. The jejunum is approximately 40% of the small bowel and the distal segment, the ileum, makes up the remaining 60%. The small intestines are where the majority of digestion and absorption occurs, with chyme and secretions being mixed and 'pushed' into contact with the absorptive intestinal lumen wall.

Normal small bowel motility consists of segmentation, which is determined by contractions of the circular muscle of the intestine. Segmentation is characterised by localised contractions of circular smooth muscle which divide the small intestine into oval segments, when the recently contracted segment contract neighbouring segments relax and so on.

The chyme is pushed towards the large intestine (colon) by cyclical rhythmical contractions called peristalsis.

Normally, regular slow waves of peristalsis occur along the entire length of the small intestine, ranging from 11-13 contractions per minute in the duodenum to 8-9 contractions towards the end of the ileum.

The duodenum tends to follow the contractile activity of the antrum of the stomach the reason for this is to prevent the reflux of contents back onto the stomach

When a bolus of material (for example food or enteral feed) is delivered to the small intestine, the intestine responds by contracting proximal to the bolus and relaxing distal to the bolus, the aim being to propel the bolus further down the intestines.

Over distension of the small bowel is characterised by a corresponding reflex, which prevent further delivery of contents in to the small intestines from the stomach. It is thought that this is controlled by the hormone gastrin, which also works to increase distal small intestine motility to alleviate the over distension.

Colonic Motility

Large bowel motility is characterised by segmental contraction with non-propulsive activity. This allows mixing the contents and maximised the time for absorption. Several times a day high-pressure propulsive peristalsis waves propel colonic contents towards the rectum. In normal subjects a meal will be left in the colon for 3 days after eaten.

Stimulation of Gastrointestinal Motility

Historically it was thought that the gastrointestinal tract was innervated by the autonomous nervous system alone. More recently studies have shown that the Enteric Nervous system (ENS) has a vital role in GI motility [654]. The ENS can act independently of the brain and controls peristalsis, local changes in blood flow and secretion of water and electrolytes [655] The ENS is an important influence on the body's immune response [655].

Neuropeptides are the neurotransmitters of the ENS, they are produced by the entero-endocrine cells. These cells extend along the entire length of the GIT and respond to changes in levels of bacterial toxins, pH, osmolarity and lipids in addition to direct contact. In addition, the production of these neuropeptides seems to be influenced by cytokines, hormones and drugs [384, 393, 394, 636].

Fasting and its effect on gastric and small bowel motility

When humans are in a fasted state, three phases of gastrointestinal motility occur:

1. Phase I – there is no activity

2. Phase II- irregular activity occurs

3. Phase III- Strong rhythmic contractions starting in the stomach spread distally. This phase is known as the migrating motor complex (MMC). It occurs every 90 minutes (range 50-140 minutes) and each contraction lasts for 5-10 minutes in any one area [384, 393, 394].

The MMC has the important role of propelling the residual of the last meal eaten into the distal part of the small bowel and colon. Failure of the MMC leads to bacterial overgrowth.

Fed State and Its effect on gastric and small bowel motility

The presence of nutrients in the stomach elicits peristaltic waves, which start in the mid stomach and propel the food from mid stomach to the pylorus. This occurs every 20 seconds. Liquids start to empty as soon as they reach the stomach. Liquids empty from the stomach much faster than solid foods. These slow waves are thought to originate from the interstitial cell of Cahal [384, 393, 394] and range from contraction activity in the jejunum at 12 contractions per minute to 8 per minute in the ileum. Small bowel contractions can be segmental or peristaltic with peristaltic waves occurring mainly in the duodenum and segmental occurring in the jejunum and ileum.

I.II Methodological Quality Criteria for Reviews of Trials

The following criteria were used when comparing the clinical trials.

Patient Selection
Were the eligibility criteria for the trial specified?

Treatment Allocation
Was the trial randomised?

Was treatment allocation concealed?

Were the groups similar at baseline with respect to the most important prognostic indicators?

Interventions
Were the interventions explicitly described?

Was the care provider blinded to the intervention?

Was the compliance acceptable in all groups?

Was the patient blinded to the intervention?

Outcome Measures
Were the outcome measures relevant?

Were adverse events reported?

Was the withdrawal and drop out rate acceptable?

Was the timing of the outcome assessment in both groups comparable?

Statistics
Was the sample size for each group described?

Did the analysis include an intention to treat analysis?

The above criteria were used as a basis when reviewing the clinical trials. If not recorded in the clinical paper an assumption can be made that it was not recorded or reported.

II. Appendices to Supplement the Methods

II.I Pilot Study

A pilot study was conducted. The purpose of this was to highlight any organisational issues, which could be encountered during recruitment for the main study. It was also to check the protocol was robust and easy to follow and adhere to.

Protocol Design

A literature search was perfomed using Medline and Cochrane databases. A

well-researched clinical trial protocol was developed.

Sample Size

N=8

Aim

To check that the protocol is robust and the trial isfeasible. All gastrointestinal cancer patients undergoing major resction were approached to enter into the pilot study.

Methods

All the appropriate ethical and research governance forms were completed in accordance with Researh Governance Framework [557].

Patients were referred to the RCT from the surgical multi-disciplinary team following the diagnosis of a suspected GI malignancy. Patients were given the information sheet (see appendix II.IV) and informed written consent (appendix II.V) was obtained.

Nutritional, biochemical and anthropometric information, both at diagnosis and prior to surgery, is collected. The patient is then randomised to either the early EN group or the standard group.

Group A (Standard therapy group)

In keeping with standard practices, patients are kept on intravenous fluids until instructed by the surgical team.

Group B (Treatment group)

In addition to standard management, these patients will commence an enteral feed via a jejunostomy within 24 hours of surgery at the rate of 10ml/hour. The rate of EN will be increased by 10ml/hour every 12 hours, to achieve full nutritional requirements by the 5th post-operative day.

Patients will be allowed to drink and eat once instructed by the surgical team, as with the standard group.

The patients were followed up daily for the first 7 days and then at day 9, 12, 15, 20 and day of discharge.

Results

The consent rate for the pilot study was 90% in the Upper GI and Hepatobilary group. The consent rate for the colorectal patients was 15%.

Twelve patients were recruited into the pilot study. The protocol was robust and well adhered to.

The mean LOHS for the enteral nutrition group was 19 days compared to 22 days in the standard group. No statistical analysis was conducted in view of the small sample size.

II.II Amendments to Study Design after Pilot Study

Recruitment was not as successful in the colorectal group. This was attributed to the fact that these patients required naso-jejunal enteral feeding tubes, which lead to a reduction in compliance. In addition there was a change in surgical technique from moving to opt to laproscopic colectomy as opposed to an open procedure. These changes in surgical procedure lead to a shorted LOHS and hence it was decided that these patients should no longer be referred to the main RCT.

There was also a lack of Intensive care beds, which lead to patients being cancelled for their major surgery. In addition, the pilot study coincided with winter and hence the annual winter bed pressures also lead to cancellations of elective surgical procedures.

To resolve these issues, the RCT was planned to be extroplotated across neighbouring hospital centre in the South East Wales Network of Upper GI surgery. The aim of this is to improve the accrual rate. Therefore the proposed sample size should be achieved in 2 years. The protocol was ammended as outlined in the current RCT.

II.III Ethical Approval

AWDURDOD IECHYD
BRO TAF
HEALTH AUTHORITY

14 October 2002

JJS/JJL

Ms R Barlow,
Senior Dietitian,
Department of Surgery,
University Hospital of Wales
Heath Park,
Cardiff.

COPY

Dear Ms Barlow,

02/4714 - A Randomised controlled trial of the effects of early enteral nutritional post-operatively in patients undergoing resection for gastrointestinal malignancy

Thank you for your letter of the 20th September 2002, regarding the above application for ethical approval.

The Acting Chairman of the Bro Taf Local Research Ethics Committee (Panel B), Mr C Weston, has confirmed that your response is satisfactory. Mr Weston has therefore taken 'Chairman's Action' to grant full ethical approval to this application.

The following documents were received together with your letter:

Patient information sheet, Version 2 dated 20/09/02
Patient consent form, Version 2, dated 20/09/02
GP Letter, Version 2, dated 20/9/02

I can also confirm that the above study has now been approved by the Risk Assessment Panel as detailed in my letter of the 8th October 2002.

I trust this is satisfactory, however, should you require any further information please do not hesitate to contact me.

Yours sincerely,

Mrs Jagjit Sidhu
Deputy Executive Officer
Local Research Ethics Committee

☎: **029 20402446/20402309**
JSidhu@bro-taf-ha.wales.nhs.uk

II.IV Patient information Sheet

To be issued on the Hospital Trust headed paper

Version 2 date 20/9/02

A RANDOMISED CONTROL TRIAL OF EARLY ENTERAL NUTRITION AFTER MAJOR GASTROINTESTINAL SURGERY

Before you decide to take part in this study you should read this information sheet carefully. It gives details of the research in which you are being invited to participate. Your doctor will also discuss the study in detail with you. If, after reading this sheet and discussing the study with the doctor you feel you would like to take part, please sign the consent form and return it to the doctor. You should keep this information sheet in order that you may refer to it in the future.

Why is this research being done?

We are doing this research to see whether nutrition given through a feeding tube is helpful in improving the ability to recover from surgery. Traditional management following surgery involves 'resting' the gut to prevent foods aggravating the site of the operation. Foods are usually introduced after approximately five to seven days. Over the past few years, new medical evidence has suggested that the early delivery of nutrients via a feeding tube given directly into the intestines may improve the ability to recover from surgery. However this evidence is not yet sufficient to persuade a radical change in post surgical practices. The trial into which you are being invited to enter will hopefully provide this evidence or clarify that we should continue with our current post surgical management.

Approximately 180 patients will be included in this study.

How is the nutrition given?

After you have consented to be in the trial, you will be allocated in to either the treatment group or the control group. If you are in the treatment group, nutrition will be given through a feeding tube inserted in your abdomen (tummy) at surgery. If you are in the control group, you will receive our current management, which is to remain 'nil by mouth' until your surgeon says that you are able to eat.

What does participation in this study involve?

The Research Dietitian will introduce herself and explain fully about the trial. If you need more time to decide this will be fully respected.

Participation in this study requires that you answer some simple questions after your surgeon has informed you that you will possibly require an operation. These questions are about your normal eating habits, weight and any weight loss and your current quality of life. This will take place in the outpatient department.

When you come in for your operation. I will meet you again, this time on the ward and I will explain step by step what the trial involves.

Before your operation, routine information will be collected about any changes in your weight and blood chemistry. You will be asked to have one additional blood test taken when you have your routine bloods checked –this is to determine your immunity levels on your blood.

If you are having any operation for a bowel problem, you will have a feeding tube passed up your nostril and into your tummy before you have your operation. This helps to ensure that the tube is positioned correctly in to the bowel before you have your operation, preventing the need to have to stay in the operating theatre longer than necessary after your operation (as would be the case if the tube was placed in theatre). This is a routine procedure that is used frequently in hospitals.

If you are having your operation for a gullet, stomach or pancreas problem, then a feeding tube will be placed into your tummy at the time of your operation. Prior to your operation you will have one additional blood test taken (this will however be taken when you have all your other tests so that you should only need one needle.) in addition you will be given a questionnaire to complete (this can either be completed at home or with the Research Dietitian or Specialist Nurse.

If you are randomised into the feeding group, nutrition will be commenced as soon as your Consultant agrees, usually within 24 hours. If you are randomised to the conventional group you will remain 'nil by mouth' for the first 3-7 days depending on your consultants instructions.

You will be monitored closely throughout your hospital stay. You will have an additional ultrasound scan after 2-3 days after your operation. This is to determine the movement in your intestines. Oral food will be introduced to you once again as soon as your Consultant is happy. The feed through the tube will be stopped when you are able to eat enough food and fluids to warrant doing so.

If for any reason you are in the control group and you are not able to eat sufficient foods at this time, nutrition will be given to you via your unused feeding tube. This nutrition once again can be given until you are able to eat enough foods.

Once you are fit enough to go home, you will be ask to answer some more simple questions similar to that already ask in the initial visits.

You will be followed-up at your routine Consultant outpatient clinic after discharge.

This clinic visits at 4 to 8 weeks will be very similar to the first visit.

Do I have to participate in the study?

Participation in the study is entirely voluntary. If you decide not to participate in this study your medical care will not be affected in any way. If you decide to take part, but then change your mind, you may withdraw from the study at any time. You do not need to give a reason for withdrawing, but it would be helpful if you could. Again, the fact that you withdraw will not affect your medical care in any way either now or in the future. Your doctor might decide to withdraw you from the study if he/she thinks that it is in your best interest to do so but he/she will discuss this with you first and will give his/her reasons for doing so.

Are there any risks or benefits to participating in the study?

In general people who receive nutrition after surgery have very few side effects. The only symptoms noted in the previous studies were nausea, which can be treated by your doctor. If you feel unwell please inform your doctor.

What happens to the information collected about me on the study?

If you agree to take part in this study, your case notes and other information collected about you during the study may be consulted by the investigator. In the information collected for the study you will be referred to only by your initials and a unique study number and never by your full name. All information will be treated in the strictest confidence.

Other information

Your General Practitioner will be informed, with your permission, about your participation in this study if you decide to take part.

The results of the study are expected to be available late in the year 2006.

Whom can I contact if I need to?

If you wish to discuss any aspect of the study with you should use the following contact numbers;

3) On-call Surgical Registrar

Via bleep from switch board

University Hospital of Wales

2920 747747

Thank you very much for considering taking part in our research. Please feel free to discuss this information with your family, friends or General Practitioner if you wish before reaching a decision.

II.V Patient consent form

Version 2 date 20/9/02

To be issued on Hospital Trust headed paper

A STUDY COMPARING TWO TYPES OF NUTRITION AFTER MAJOR SURGERY

1. I (name of patient)

Of (address of patient)

Voluntarily agree to participate in this study.

I confirm that I have been given a full explanation of the purpose of the study by my doctor and/or the lead investigator and have had adequate opportunity to ask questions. I have been made aware of the procedures involved, any potential risk to my health and well-being and what is expected of me during the study.

I understand that I am free to withdraw from this study at any time, without explanation, and that such withdrawal will not affect my future treatment.

I understand that all reasonable steps will be taken to protect my confidentiality and that my name will not be disclosed to any unauthorised person or to be referred to in any report concerning this study.

I agree to my doctor informing my GP about my participation in the trial.

SIGNATURE OF PATIENT

Signed ----------

Dated ----------

Name ----------

SIGNATURE OF INVESTIGATOR

Signed ----------Date ----------

SIGNATURE OF WITNESS

Signed ----------

Dated----------

Name----------

II.VI Case Report Forms

At Diagnosis – Data Collection

Nutritional Assessment

Kcal/day	Protein/day	Weight

DIETARY

Pre illness weight	Pre illness BMI	%weight loss	BMI	Appetite normal	y	n

Taste changes	Swallowing/chewing difficulties

Anthropometric

TSF		MUAC		Hand Dynamometry		85% less than normal	y n

Biochemical

Albumin		Na		K		Urea		Creatinine		Mg	
Selenium		PO_4^-		Calcium		Alb		Lymphocyte		Hb	

Socio-economic Assessment

Salary Range	<£12000	£12000 - £16000	£16000 - £20000	£20000 - £25000	£25000 +

Demographic Information

Male	Female	Age	Postcode

Quality of Life Questionnaire

PMH

Diagnosis

Occupation

Units Alcohol/week	Ex-drinker	Heavy alcohol use	Alcohol dependency
Cigarettes/day	Ex-smoker	For how long stopped smoking?	

Inpatient Data Collection

Nutritional Information

Height | TSF | MUAC | Handdynometry | 85% normal | y | n

NA | K | Urea | Creatinine | Magnesium

PO_4^- | Selenium | Calcium | Albumin | Hb

Lymphocyte | Glucose | Copper | Zinc | Fe

Immunological Information

White cell count | CRP | Pyrexial | Apyrexial | CD11b

Theatre information

Theatre time	Blood loss	Asa grade	Diagnosis	Surgical procedure	Drugs in theatre	IV fluids in theatre	UO in theatre

Post Op Monitoring Form 1

Day	WaRD	Volume of feed	Rate of feed	Oral Fluids	Oral Diet	Temperature	WCC	CRP	Total lymphocyte count	U + E's	Albumin	N2 bal	GLUC	MG P04	HB
1															
2															
3															
4															
5															
6															
7															
9															
12															
15															
20															
Discharge															

Post Op Monitoring Form 2

DAYS	NAUSEA	VOMITING	NG ASPIRATES	DIARRHOEA	FLATUS	CONSTIPATION	ABDOMINAL DISTENSION	PATIENT REFUSING FEED	URINE OUTPUT	FLUID BALANCE	IV FLUIDS
1											
2											
3											
4											
5											
6											
7											
9											
12											
15											
20											
DISCHARGE											

XX

Post Op Complications Monitoring Form

DAY	PAIN SCORE	ANALGESIA REQUIREMENT	WOUND INTACT	WOUND INFECTION	PE	CHEST INFECTION	ANASTOMOTIC LEAK	CONSERVATIVE MANAGEMENT	THEATRE NEEDED	DVT	MOTILITY	WEIGHT
1												
2												
3												
4												
5												
6												
7												
9												
12												
15												
20												
DISCHARGE												

POST-OP DRUGS MONITORING FORM

DAY	ENTERAL DRUGS	IV DRUGS
1		
2		
3		
4		
5		
6		
7		
9		
12		
15		
20		
DISCHARGE		

Health Economy Data Collection

Theatre operation time

Jejunostomy insertion time

Post Op Dietitian Time

Length of Hospital stay

Length of ITU stay

Length of HDU stay

Control Group IV Drugs

Volume

Dose

Duration

Treatment Group IV Drugs

Volume

Dose

Duration

Enteral Drugs

Patient Developed infection	y	n		What Type?
If yes antibiotics needed	y	n		What Type?
Chest physio needed	y	n	Duration	
			Number of visits	
Wound infection	y	n		
Special dressing needed	y	n	If yes what	
Special mattresses needed	y	n	If yes what duration	

Changes in drug prescription on discharge:

II.VI Letter to General Practitioner

To be issued on the Hospital Trust headed paper

Version 2 date 20/9/02

LETTER TO GENERAL PRACTITIONER

Date

Dear Dr.....

Re: A RANDOMISED CONTROL TRIAL OF EARLY ENTERAL NUTRITION AFTER MAJOR GASTROINTESTINAL SURGERY

Your patient _____

Has agreed to participate in a randomised controlled clinical trial to study the effect of enteral nutrition on surgical outcome.

The study is as detailed in the attached Patient Information Sheets and the study schedule is reproduced overleaf for your information. Briefly, patients will be randomised to receive either enteral nutrition via a feeding tube of remain nil by mouth until passage of flatus.

Your patient has been given a copy of the Patient Information leaflet and has given written informed consent (copy enclosed for your records).

If you have any queries concerning this trial please do not hesitate to contact me at the number below.

Signed:_____ Date:_____

RACHAEL BARLOW

RESEARCH DIETITIAN

DEPARTMENT OF SURGERY, UNIVERSTITY HOSPITAL OF WALES

02920 744294/bleep 07623 906116

II.VII Nutritional Composition of Enteral Feeds

Nutritional information/100ml	Nutrison Standard	Osmolite	Perative
Energy (kcal)	100	101	131
Protein (g)	4	4	6.7
Carbohydrate (g) of which sugars	12.3 1.0	13.6 0.69	17.7
Fat (g)	3.9	3.4	3.7
Fibre (g)	0	0	0
Sodium (mmol)	4.3	3.83	4.5
Potassium (mmol)	3.8	3.79	4.4
Osmolality (mosm/kg H_20)	310	288	308

Nutritional information/100ml

III. Appendices to Supplement the Results Chapter

III.I Supplementary Baseline Results

Table III.I.I presents the number and percentage of patients with a differing surgical procedure in the current RCT with a pre-operative weight loss of more than 10%. The results suggest that more patients undergoing gastrectomy (partial, subtotal and total) lost more than 10% weight loss prior to surgery than other types of surgeries

Table III.I.I Number of patients by surgical procedure with a pre-operative percentage weight loss greater than 10%

Type of Surgical Procedure	N	%
Transhiatal Oesophagectomy	1	5.5
Ivor Lewis oesophagectomy	10	34
Partial gastrectomy	1	50
Subtotal Gastrectomy	8	62
Total gastrectomy	6	43
PPPD	8	42
Total pancreactectomy	2	33
Total of study population	36	38

Table III.I.II presents pre-operative percentage weight loss by gender. It appears that women lose more weight pre-operatively with 22% of females losing more than 16% of the pre-illness weight in the 3 months prior to surgery.

Table III.I.II Pre-operative weight loss compared by Gender

Percentage weight loss	Male N (%)	Female N (%)	Test Statistic (P)
Less than 5%	35 (55)	11 (34)	CHI=13.23 (0.01)
6-9%	8 (12.5)	8 (25)	
10-15%	18 (28)	6 (19)	
16-20%	2 (3)	1 (3)	
More than 21%	1 (1.5)	6 (19)	

The results for pre-operative Nutritional Risk Index are similar to pre-operative percentage weight loss. Significantly more women were either moderately or severely at risk of malnutrition as compared to the men. The results are presented in table III.I.III.

Table III.I.III Results of male and female pre-operative nutritional risk index

NRI	Male N (%)	Female N (%)	U (p)
Severe PEM	4 (6.7)	6 (21.4)	U=636 (0.004)
Moderate PEM	2 (3.3)	4 (14.3)	
Borderline PEM	54 (90)	18 (64.3)	

PEM- Protein Energy Malnutrition

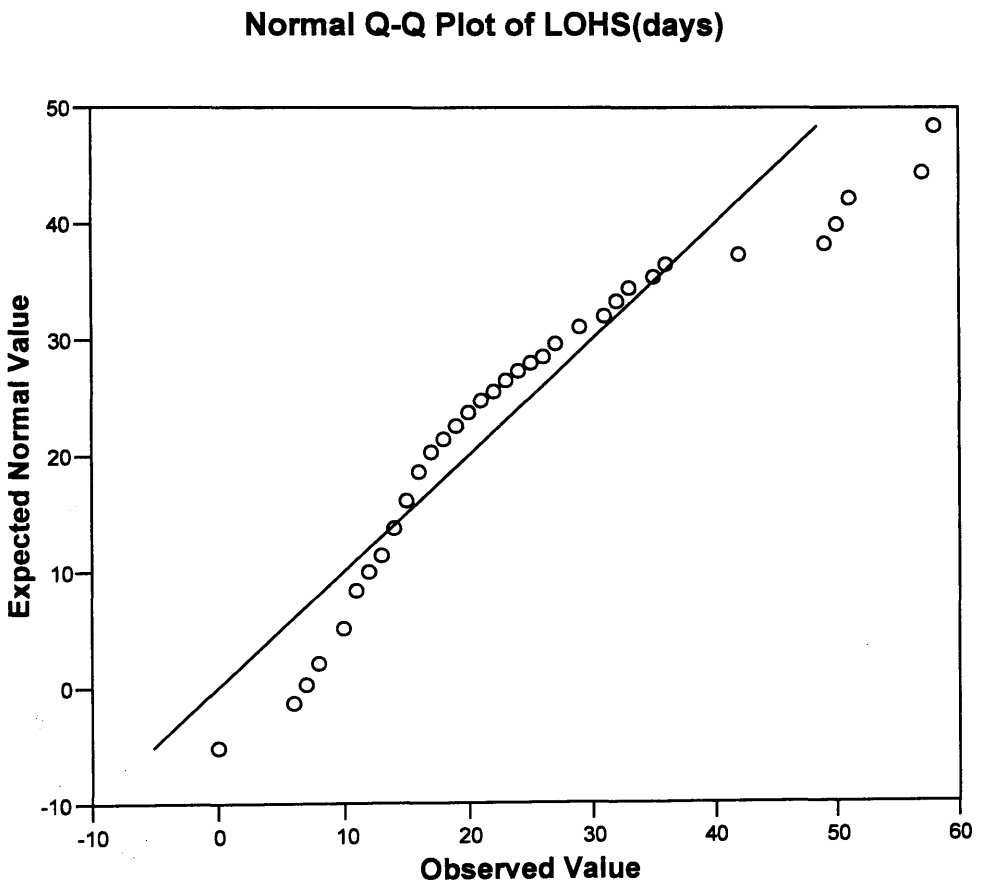
Table III.I.IV Results of Baseline Biochemical Parameters for the two randomisations groups

	STD Group	EEN group	Reference range
Albumin (g/l)	41	41	35-50
C reactive protein (mg/l)	7	8	0-10
Haemoglobin (g/dl)	32	36	13-18
WCC 10^9 /litre	35	46	3.5-11.0
Calcium mmol/L	2.3	2.3	3.5-11.0
Selenium umol/l	0.7	0.7	0.8-1.4
Magnesium mmol/L	0.8	0.8	0.65-1.05
Phosphate mmol/L	1.19	1.09	0.87-1.45
Sodium mmol/L	140	138	135-150
Potassium mmol/L	4.0	4.1	3.3-5.1
Urea mmol/L	5.0	5.0	1.7-8.3
Creatine umol/l	80.8	85.0	44-101

III.II Supplementary Results for Primary Outcomes

As discussed in the results chapter the data for length of hospital stay was not normally distributed. The QQ plot is presented below

Figure III.II.I QQ plot showing the distribution of data for LOHS



III.III Supplementary Results for Secondary Outcomes

III.II.II Supporting Information for Cost Analysis

Table III.III.I Cost of Treating a Chest infection

Cost	Cost per day	Justification of Cost
Medical time	20 mins/day= £40	Time for junior medical team to review patient on ward round daily
Nursing time	30 mins/day= £15	Extra nursing time for administration of drugs +/-oxygen, taking patient to x-ray
Chest X-Ray	£40 one off cost	Only one X-Ray was included
Physiotherapy	30 min/day =£20	Top of scale band 7 physiotherapist
Antibiotics (Intravenous)	£10-£32/day	BNF price of Intravenous clarithomycin
Total	£115-£147	

BNF-British National Formulary

Table III.III.III Cost of Treating a Wound infection

Cost (£)	Cost per day	Justification of Cost
Medical Time	20 mins/day= £40	Time for junior medical team to review patient on ward round daily
Nursing Time	30 mins/day= £15	Nursing time to dress wounds (sterile technique)
Dressings	£10 /day	BNF price Kaltostat Packings £6.78 Tegaderm £2.34
Antibiotics	£10- £32	BNF price of Intravenous clarithromycin. IV used as patient NBM
Total	£75- £107 per day	

BNF-British National Formulary

Table III.III.III Cost of treating an anastomotic Leak

Cost (£)	Cost per day	Justification of Costs
Critical Care stay	£0-£1000	The range in cost is dependent on whether the patients are readmitted to Critical care. The WAG (2005) figure for cost of 1-day critical care stay is £1000.
Medical Time	20 mins/day= £100	The cost of Consultant Surgeon and the junior medical team to review patient on daily ward round
Nursing Time	30 mins/day= £25	The cost of critical care stay includes intensive monitoring and nursing care of the patient. However, this is the extra care for managing a patient with an anastomotic leak either on a ward or on critical care. This figure was calculated after asking the senior nurses on the wards to estimate the time taken per day.
Return to theatre	2 hours @ £300=£600*	This is an optional cost and is dependent on whether the patients necessitate a return to the operating theatre. All patients in this RCT returned to theatre for exploratory surgery after developing an anastomotic leak.
Antibiotics	£10- £32	BNF price of Intravenous antibiotics.
Radiology Costs	Gastrograffin swallow* £150 Chest X-ray* £40	To diagnose an anastomotic leak, patients often have a gastrograffin swallow and a minimum of one Chest X-Ray. These costs are taken from the WAG (2005)
Total	£135-1157 per day	

*refers to one off costs for treating an anastomotic leak such as returning to theatre, gastrograffin swallow and chest X-Ray which for simplicity are not included in the costs for treating an anastomotic leak.

III.III.II Supporting Information for Health Related Quality of Life

Figure III.III.I Time Series of Health related Quality of Life Factor-General Health Status by randomised group

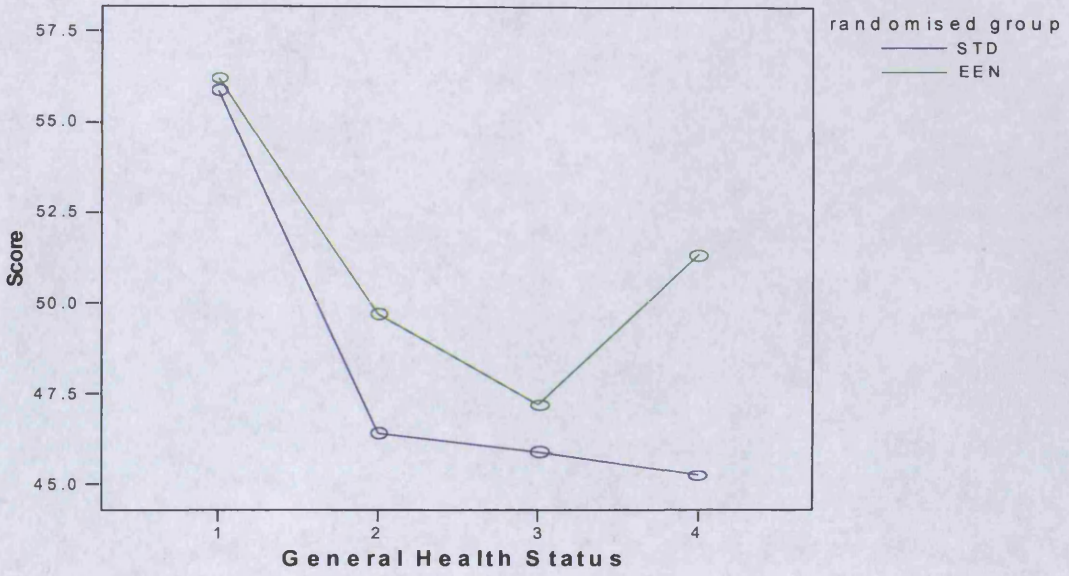


Figure III.III.II Time Series of Health related Quality of Life Factor - Physical Role

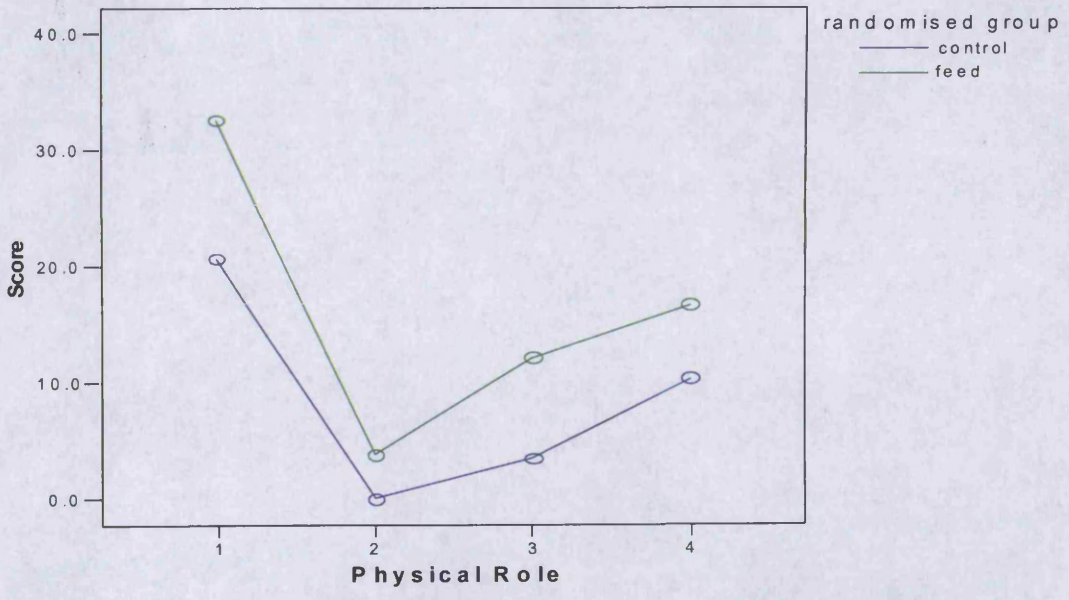


Figure III.III.III Time Series of Health related Quality of Life Factor-Vitality

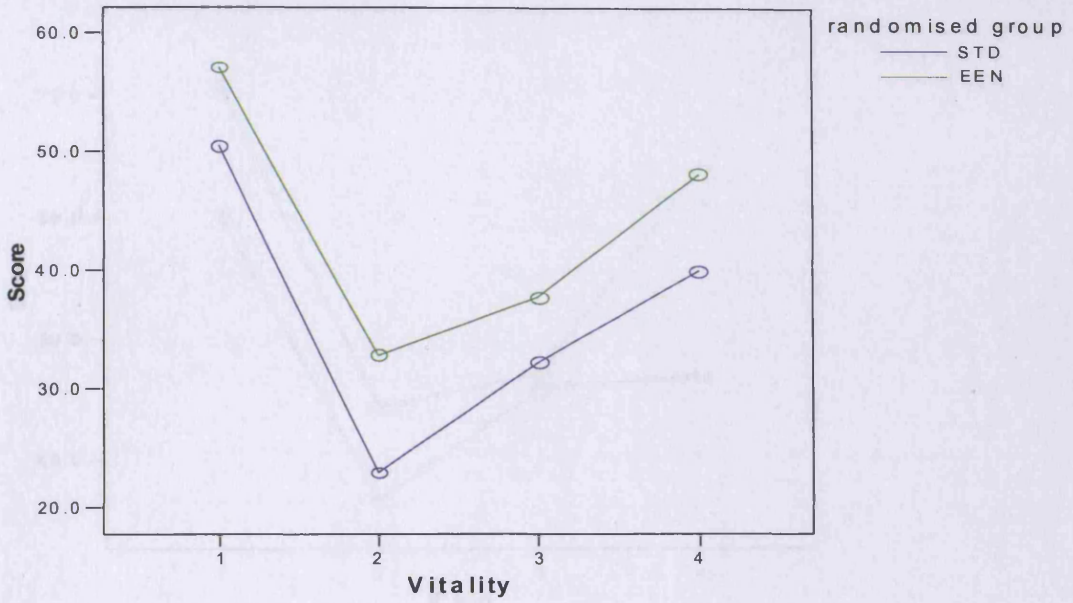


Figure III.III.IV Time Series of Health related Quality of Life Factor - Physical Role

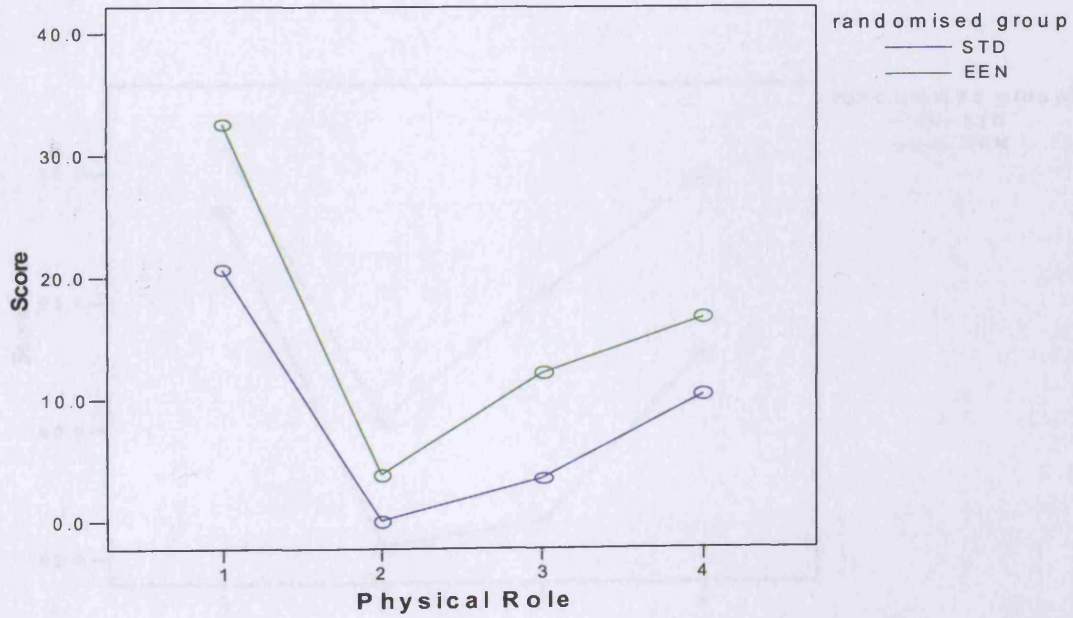


Figure III.III.V Time Series of Health related Quality of Life Factor- Pain

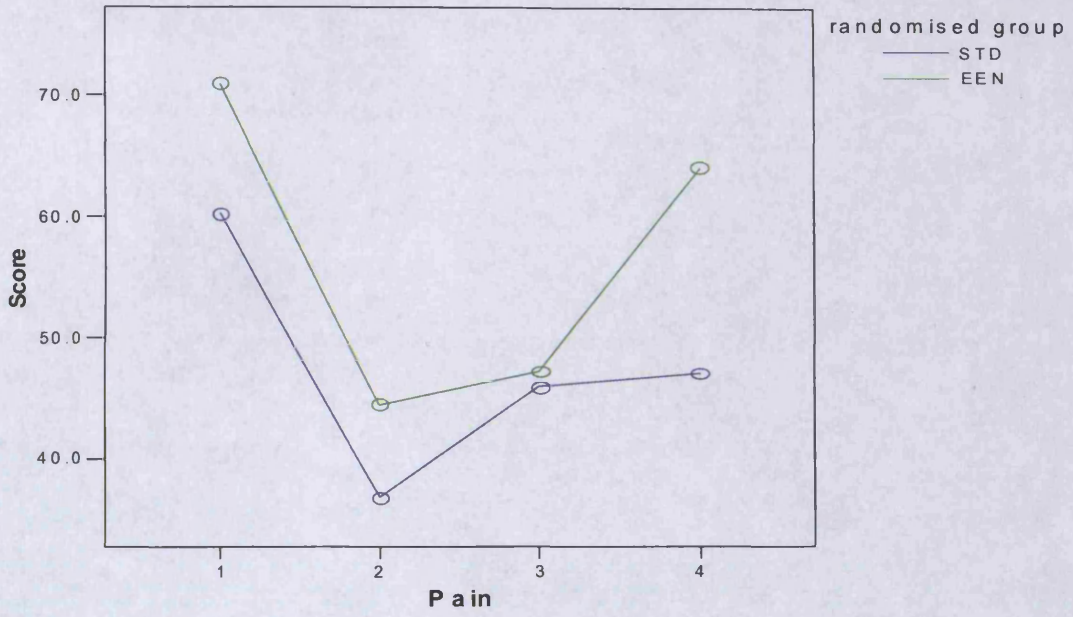


Figure III.III.VI Time Series of Health related Quality of Life Factor Mental Health

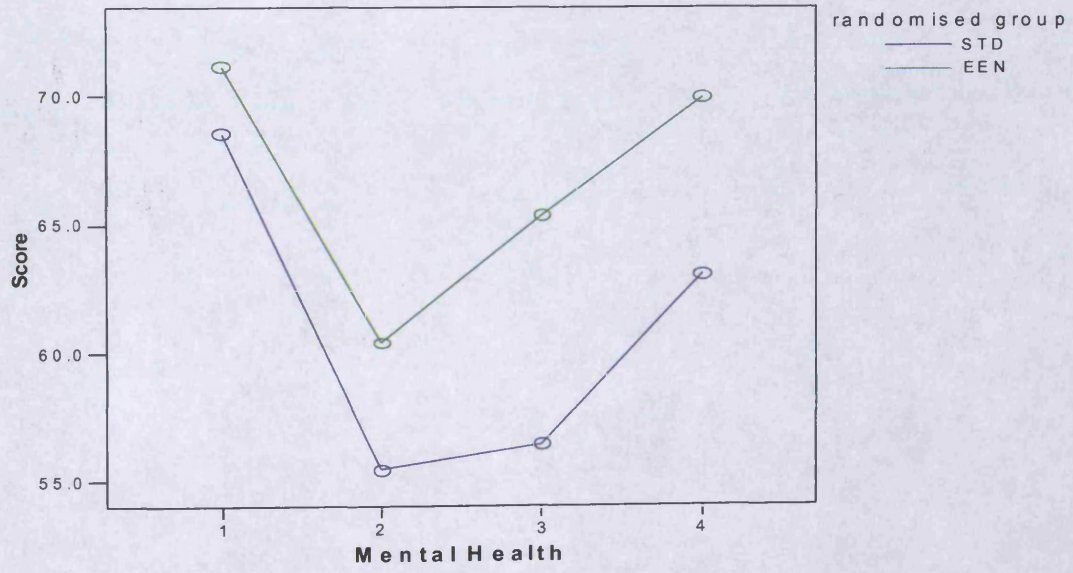


Figure III.III.VII Time Series of Health related Quality of Life Factor - Social Functioning

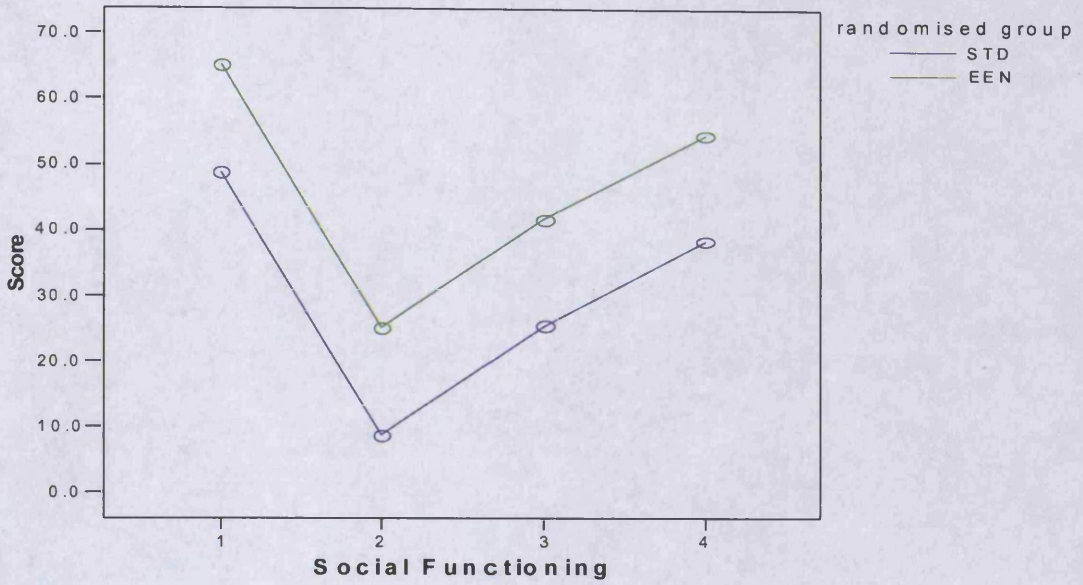
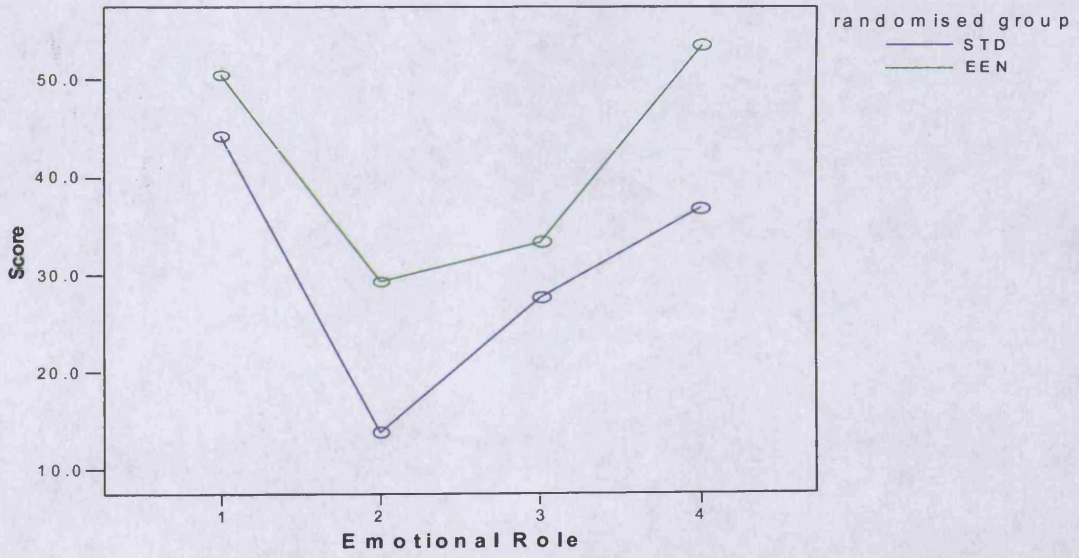


Figure III.III.VIII Time Series of Health related Quality of Life Factor- Emotional Role



AUGIS

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at The Royal College of Surgeons of England
35/43 LINCOLN'S INN FIELDS
LONDON, WC2A 3PE

23 October 2007

Dear Ms Barlow,

BJS Best Paper Prize- AUGIS Scientific Meeting, Cardiff 2007.

We are writing to congratulate you on your winning presentation during the Best Paper Session at the recent AUGIS meeting in Cardiff.
The 10 abstracts featured in the BJS Best Paper category scored the highest marks from the abstracts submitted for the conference, therefore to have been selected as the BJS prize winner is a true achievement. Your success was reflected in the extremely high standard in which your paper was presented.

Please find enclosed a token of your achievement.
Thank you for all the hard work - congratulations again on a job well done.

Kind Regards

Mr Merv Rees
AUGIS President

Mr Rowan Parks
Scientific Committee Chair