Quality of Life in Intestinal Failure

By

By Alison Chambers

Department of Human Nutrition

Thesis Submitted for the degree of doctor of philosophy

Queen Mary College University of London

2011

Abstract

Aims/objectives: The objectives of this research were to investigate and compare aspects of Quality of Life (QoL) in adult patients who require HPN, in adult patients who have pseudo-obstruction, and in carers of, and children on, HPN.

Methods: Demographic data, clinical parameters and current symptoms were collected and analysed. Generic QoL questionnaires were applied to the above groups.

Results: HPN patients have significantly lower QoL than the rest of the UK population, report increased levels of bodily pain, anxiety and depression, a reduction in physical functioning, social functioning, general health, vitality and satisfactory levels of mental health and emotional functioning. Aspects of QoL improve over the first 6 months on HPN. Pseudo-obstruction has a negative impact on all aspects of QoL when compared to a normal population. A previous intestinal resection and opiate use had a negative impact on aspects of QoL. Carers of a child on HPN seek more social support and use more positive reappraisal coping strategies, more planful problem solving and less distancing than the controls and a higher level of psychiatric disorder is also seen. Children on HPN have a poorer functional status than those not on HPN, and there is a correlation between level of child dysfunction and parental general health. Families caring for a child on HPN function within normal and healthy parameters.

Conclusions: Our studies indicate that the loss of intestinal function does have a negative impact on aspects of QoL but patients make adjustments to meet everyday requirements, even if it produces limitations with which these persons have to live by.

Declaration

This is to certify that this thesis comprises only my original work towards the PhD, due acknowledgement has been made in the text to all other material used.

This thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Alison Chambers

TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

AIDS Acquired Immune Deficiency Syndrome
BANS British Artificial Nutrition Survey
BAPEN British Association for Parenteral and Enteral Nutrition
CBCL Child Behaviour Check List
CIIP Chronic Idiopathic Intestinal Pseudo-obstruction
COREC Central Office for Research Ethics Committee's
CVC Central Venous Catheter
EN Enteral Nutrition
EQ5D Euro QoL 5 Dimensions (see appendix 3)
- **MB** Mobility
- **SC** Self Care
- **UA** Usual Activities
- **PD** Pain or Discomfort
- **AD** Anxiety or Depression

ESPGHAN European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FAD Family Assessment Device (see appendix 7)
FSIIR Functional Status Short Version (see appendix 6)
GHQ General Health Questionnaire (see appendix 5)
GI Gastro Intestinal
GP General Practictioner
HADS Hospital Anxiety and Depression Scale (see appendix 2)
HDU High Dependency Unit
HEN Home Enteral Nutrition
HIV Human Immunodeficiency Virus
HPN Home Parenteral Nutrition
HRQoL Health Related Quality of Life
IBD Inflammatory Bowel Disease
IBDQ Inflammatory Bowel Disease Questionnaire
ICU Intensive Care Unit
ID Intractable Diarrhoea
IF Intestinal failure
IQ Intelligence Quotient
ITx Intestinal Transplant
IV Intravenous
LCFA Long Chain Fatty Acids
LCT Long Chain Triglycerides
LREC Local Research Ethics Committee
MCFA Medium Chain Fatty Acids
MCT - Medium Chain Triglycerides
MDT Multi Disciplinary Team
MMC Migrating Motor Complex
MREC Multi Research Ethics Committee
NASA National Aeronautics and Space Administration
NCG National Commissioning Group
NHS National Health Service
NNS Nutrition Nurse Specialist
PICC Peripherally Inserted Central Catheters
PINNT Patients on Intravenous and Nasogastric Nutrition Therapy
PN Parenteral Nutrition
QoL Quality of Life
QoLI Quality of Life Index
QOLID Quality of Life Instruments Database
SB Small Bowel
SBS Short Bowel Syndrome
SBTx Small Bowel Transplant
SF36 Short Form 36 Questionnaire (see appendix 1)
- **PF** Physical Functioning
- **RP** Role-Physical
- **BP** Bodily Pain
- **GH** General Health
- **VT** Vitality
- **SF** Social Functioning
- **RE** Role-Emotional
- **MH** Mental Health

SIP Sickness impact Profile
SL Structured lipids
SMOF Soybean, Medium-chain triglycerides, Olive and Fish oils
TM Telemedicine
TPN Total Parenteral Nutrition
WHO World Health Organisation
WOCQ Ways of Coping Questionnaire (see appendix 4)

Acknowledgements

Firstly I would like to thank my supervisor Professor Jeremy Powell-Tuck for encouragement and guidance and also The Whitechapel Society and Calea UK Limited for providing funding.

I would also like to thank all the patients and families who volunteered for these studies and made them possible.

Thank you also to Clare Soulsby, Eleni Athanasakos and all the friends I made along the way – particularly all the magical minds in The Wingate Institute Fellows Room 101.

Lastly I would like to say thank you (Ευχαριστώ) to my husband Stamatis Kapetanios for generally putting up with me and giving me the courage to understand statistics. Thank you to my twin sister and best friend - Suzie - for supporting me throughout in everyway possible. I really do not think I could have completed this without either of you - I love you both very much.

I would like to dedicate this thesis to Samuel Le Marechal – the best God son in the whole world.

1.0 Introduction

It is well known that eating related pleasures go beyond nutrition (1); food is more than just nourishment and it is often the central focus of some of the most important moments and events in our life. Indeed the Greek philosopher Epicurus articulated this belief when he wrote "The root of all pleasures is the satisfaction of the stomach" (Epicurus c. 341-270BC), although it is undeniable that losing the ability to eat in ancient times would have eventually resulted in death, this quote identifies the significance of the multidimensional role that food plays in our lives. However, the advancement of medical science has allowed the therapeutic provision of nutrients to people who no longer have the full capacity to eat, posing the questions;

- How do people cope with the medicalisation of nutrition/food?
- Does loss of the enjoyment of eating impact on the quality of one's life?

The purpose of this body of work is to present research that attempts to examine and answer aspects of the above speculations and notions.

To this end, three different groups of people with intestinal failure were studied

- Adult Home Parenteral Nutrition (HPN) patients
- Paediatric HPN patients and their carers
- Chronic Idiopathic Intestinal Pseudo obstruction (CIIP) patients

Food is defined as anything ingested which has nutrient value and diet is that food and drink which is consumed or provided on a regular basis (2). These groups were chosen for study as their medical situation (intestinal failure) compromised both their diet and ability to eat food.

1.1 Intestinal Failure

The term intestinal failure was originally defined by Fleming and Remington in 1981 and implied a functional rather than an anatomical definition, resulting in a reduction of the functioning intestinal/gut mass below the amount necessary for adequate digestion and absorption of food (3). Paediatric authors have also described it as any condition in which the gastrointestinal (GI) tract fails to satisfy the nutritional and fluid requirements of the body (4) to allow for growth (5).

However this definition does not take into account disease aetiology. In 2006 an international group of experts tried to address this issue by proposing that intestinal failure results from obstruction, dysmotility, surgical resection, congenital defect, or disease associated loss of absorption and is characterised by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balance (6).

In 2002 a novel classification of intestinal failure was devised which describes 3 different types of IF (7):

Type I – this type of Intestinal Failure is short-term (days/weeks) and self limiting, where the gut can not be accessed for feeding via the enteral route. The majority of patients will be normal to moderately malnourished and the majority of the feeding will be by the parenteral route, but partial enteral feeing may be possible.

Type II – Type II is IF in severely ill patients with major resection of the bowel. Septic, metabolic and nutritional complications may be present, requiring multidisciplinary intervention with metabolic and nutritional support to permit recovery.

Type III – Type III is chronic IF requiring long term nutritional support (7)

More recently in 2008, the Strategic Framework for Intestinal Failure and Home Parenteral Nutrition Services for England expanded on these definitions and included information about where these type of patients should be treated (http://www.specialisedcommissioning.nhs.uk/index.php/key-documents/intestinal-failure-and-home-parenteral-nutrition/)(8).The report goes on to state that intestinal failure comprises a group of disorders with many different causes, all of which are characterised by an inability to maintain adequate nutrition via the intestines. It is characterised not only by the inability to maintain protein-energy, but also often in difficulties in maintaining water, electrolyte or micronutrient balance, particularly when there has been a major loss of length of the small bowel. If it persists for more than a few

days it demands treatment with the intravenous delivery of nutrients and water – parenteral nutrition (8).

1.1.1 Causes of Intestinal Failure

Four major underlying causes can be identified:

- Short Bowel Syndrome (SBS), defined as intestinal failure resulting from massive resection of the small intestine (9) or when there is less than 200cm of bowel remaining. It can be congenital (e.g. intestinal atresia) or acquired (resulting in surgical resection of the bowel) (10).
- Total parenchymal bowel disease (e.g. Crohn's disease)
- Motility disorders (e.g. pseudo-obstruction and visceral myopathy)
- Small bowel fistulation causing premature loss of enteric content (11).

All these disorders result in devastating losses of GI function.

1.1.2 Complications of Intestinal Failure

Untreated intestinal failure eventually leads to starvation or severe undernutrition caused by caloric and nitrogen deficiency. It may also result in fluid, electrolyte, mineral, vitamin and trace element deficiencies. This can be due to lack of adequate dietary intake, poor or absent nutrient absorption, increased intestinal losses, and a potential increase in energy requirements if an active disease is present. Intestinal failure can be temporary or permanent. In the past if intestinal failure was deemed to be irreversible, such patients were chronically malnourished, often unable to work or enjoy normal social activities and sometimes confined to hospital for indefinite periods, or they died (12). One social worker even referred to these individuals using the unfortunate epithet "nutritional cripples" (13).

Consumption of food provides the body with essential nutrients. Requirements for nutrients vary with age, gender and at times of physiological adaptation, for example during pregnancy, lactation, growth and during illness. Moreover, nutritional insufficiency during different stages of development can have varying consequences.

Perhaps the most important difference between adults and children is that adult nutritional requirements must meet the basal energy needs for maintaining the body's physiological functions, whereas paediatric nutritional requirements are imposed by the basal energy needs in addition to the demands of essential brain and linear growth. This can be obviously demonstrated by the reality that an adult can, if supplied with water alone, survive starvation for many weeks whereas a premature infant will only withstand starvation for 4 days (14), moreover, there are fundamental differences in the nutritional demands of the growing infant when compared to those of the older child or adult (15).

Malnutrition at any age will increase the risk of morbidity and mortality - if it occurs in early childhood it can also result in failure to thrive (16) short stature and impaired neurological development that will decrease performance at school (17) and is associated with severe and prolonged episodes of infection (18). Persistent nutrient deficiency in childhood can result in growth and sexual maturation suppression, highlighting the central importance of nutrition to a child's current health and the ability to reach their full potential for growth and neurocognitive development. Any sustained interruption to nutrition, if not treated early can result in irreversible damage to a child's development (19).

1.1.3 Effects of Intestinal Failure on Growth and Development

Growth occurs in 3 phases: infancy, childhood and puberty (adolescence) (20). Growth failure is the cessation, retardation or impairment of linear growth, characterised by a deceleration of growth velocity, or a fall in the percentile channels for height and weight in any of these three phases. More specifically it can be defined as height or weight below the third centile for age (21) and is usually associated with delayed skeletal or bone age.

GI disease frequently leads to growth failure from impaired nutritional status in children (22). Variation in both weight loss and nitrogen balance is accounted for by two factors, the previous nutritional status of the infant and the degree of ongoing stress (23),

therefore recognition of the underlying intestinal disorder, with appropriate therapy and dietary counselling for nutritional restitution, are important approaches in reversing growth retardation so that the child can achieve full growth potential (22). The role of nutrition in growth must not be underestimated, in one study of Mexican children growth failure was not related to frequency of diseases (including infection, fever and hepatitis), but seemed to be the result of chronic under-nutrition (18).

1.1.4 Effects of Intestinal Failure on Neurological and Cognitive Development

Cognitive functions may be conceptualised as those constituting the neural processes necessary to support the flexible use of information in the execution of adaptive, goal-directed behaviour (24). During the first 3 years of life, child development is dynamic and involves the maturation of interrelated cognitive and physical functions. A child's brain rapidly develops through generations of neurons, synaptogenesis, axonal and dendritic growth, each of which build upon each other. Nutrition provides the building blocks for brain development thus it has a strong influence on cognitive and fine and gross motor skill development (25).

Although most early research on nutrition and mental development in humans concerned severe protein energy malnutrition (26), animal studies have made important contributions to understanding the role of nutrition in the development and operations of the brain, by allowing manipulations and controls that would not be possible in similar studies conducted in humans (24).

There is evidence linking many nutritional deficiencies to deficits in cognition. In 1995 Grantham McGregor published a review on the effect of severe malnutrition on mental development (27). The author identified 14 studies in which malnourished children were compared with reasonably well matched controls. Severely malnourished children demonstrated marked behavioural abnormalities in the acute stage, displaying more apathy, less activity, and less environmental exploration both in quantity and complexity, than with children who were ill with other diseases. Formerly malnourished children

were found to have poorer cognitive function, school achievement and behaviour differences, neurological soft signs and poorer fine motor performance when compared with controls (28). The author goes on to report in a further publication that severe growth retardation between 12 and 24 months of age was associated with a ten point deficit in IQ on the Wechsler Intelligence scale for children (29).

The mechanisms linking malnutrition to poor development are not known with certainty but must arise through changes to the brain's anatomy or function (26). During brain development, changes in the availability of nutrient supply may result in disturbances of specific brain and behavioural functions, through their selective effect on some of these systems (24) including:

- Functional interactions between the prefrontal cortex, hippocampus and amygdala
- The ability to flexibly apply or generalise acquired knowledge in novel situations
- The ability to flexibly switch between different behavioural tendencies
- The ability to flexibly adapt to new situations and to change behaviour with changing task demands

Another mechanism known as the "functional isolation hypothesis", suggests that lack of dietary energy leads to reduced activity levels, which in turn leads to reduced exploration and subsequently results in developmental delays (30).
Children's developmental levels are extremely low in the acute stage of malnutrition, but generally improve during recovery in all areas of development. Nutritional supplementation has been associated with an increase in children's activity levels and an improvement in development (30). But, if the nutrient deficiencies continue over a long period and the child's behaviour remains abnormal, it is possible that acquisition of skills will be slow eventually leading to irreversible cognitive deficits and behavioural change, indeed, electro-physiological abnormalities have been found in children several months after recovery from severe malnutrition (27).

Although there is consistent evidence of growth retarded children having cognitive deficits it would be incorrect to attribute the entire deficit to poor nutrition or infection as

environmental and social variables are confounding, In fact in one series of paediatric HPN patients, 2 of the children were mentally gifted and attended special schools because of their advanced capability (31).

Most cases of short bowel syndrome in childhood occur in the newborn period when the brain is still increasing rapidly in size and in the complexity of its interneuronal connections. More than 90% of infants and children survive after extensive bowel resection (32). Consequently, neurodevelopment may be adversely affected by prolonged under-nutrition at this sensitive stage. There are often adverse neuro-developmental effects from prolonged admission to hospital. Not surprisingly, many children exhibit developmental delay during the course of short bowel syndrome, but subsequently improve (33).

1.1.5 Management of Intestinal Failure

The main goals of medical therapy in the adult are the immediate provision of nutritional needs to meet requirements and promote weight gain (if necessary), to keep the patient out of the hospital (to minimise institutionalisation) (34) and for the patient to return to society i.e. resume work and a normal lifestyle – or as normal of one as possible. These goals are the same in paediatrics, but also include provision for growth (35).

Adequate nutrition support must provide both macro and micro nutrients (to prevent malnutrition and specific nutrient deficiencies), sufficient fluid (to prevent dehydration), and to correct and prevent any acid-based disturbances (10). It is important to remember that some patients develop a protracted dependence on PN (36) and these patients may require nutritional support for a substantial portion – if not the remainder of their lives (37).

In addition to providing extra food and food/nutrient supplements there are 2 main types of artificial nutritional support available to those suffering with intestinal failure:

- Enteral feeding (EN) – The provision of liquid food administered via a tube into the stomach or intestine.

- Parenteral feeding (PN) – The intravenous administration of nutrients, (an aqueous food formulation) (38).

The choice of nutritional support is dependant on the cause and degree of intestinal failure. Both methods bypass the normal processes of eating, chewing and swallowing and can be administered at home. Enteral feeding is cheaper and safer than PN and is preferred if the GI tract is functioning sufficiently (39). Patients may require a varied combination of both EN and PN according to the degree of dysfunction of their intestinal tract (40).

The challenge of nutritional support is to devise a nutritional regimen that will not only support weight gain and maintenance, but also provide an optimal developmental internal milieu for the brain and other organs. PN can be seen as a substitutive technique in gut failure. It must be remembered that nutrition support does not cure non nutritional diseases (41).

Intestinal transplantation (ITx) is a surgical option for both adult and paediatric patients with irreversible intestinal failure (42;43). Complications of IF treatment are the main indications for transplantation. On the basis of the relative safety and efficacy of ITx, HPN is still considered the primary treatment for chronic intestinal failure (44).

1.1.6 Oral Intake

The parenteral method of feeding is un-physiological as the feeds are typically infused continuously (as opposed to intermittent ingestion of solid food at meal times), sometimes nocturnally, and the nutrients bypass all of the GI tract which is normally involved in the regulation of appetite and food intake (45;46) The effects of parenteral nutrition (and the macronutrients within it) on hunger and satiety remain poorly understood (47).

Disturbances in appetite sensations may occur in people receiving PN, and this is thought to be partly due to 2 main factors.

Firstly when nutrients are administered intravenously, the cephalic phase response that is normally elicited by the presence of food in the upper GI tract is absent. The cephalic response is defined as a myriad of pre-absorptive changes in thermogenesis, metabolite and hormone concentrations that follows the oral ingestion of food (48). It has been reported that PN is less effective in relieving appetite sensations than food intake (49-52) and proposed that this may be due (in-part) to the bypassing of the cephalic phase.

Secondly, when nutrients are infused intravenously they may fail to generate endogenous gut signals which typically follow oral food ingestion (53). The GI tract elicits numerous signals regulating food intake and satiety (54) The release of these satiety signals are induced by the presence of nutrients in both the stomach and the small intestine (55-57). Examples of these gut derived peptides include ghrelin, peptide YY (PYY), cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1). PYY, CCK and GLP-1 have an anorexic effect, whereas ghrelin is orexogenic. Recently Murray et al (47) demonstrated that intravenous infusions of carbohydrate (10% dextrose), lipid (10% Intralipid) or mixed protein carbohydrate (PN) in stable HPN patients had no affect on subjective symptoms of hunger, satiety or nausea. Ghrelin levels decreased significantly during the dextrose and PN infusions and the lipid infusion led to a significant decrease in PYY, however the changes in peptide levels were not associated with changes in appetite and the authors suggest that ghrelin antagonists and PYY agonists may not be viable targets for the treatment of distressing symptoms of hunger in HPN patients.

Stratton et al published several abstracts (1998-1999) relating to the impact of PN on appetite, summarised in Stratton and Elia 1999 (53) and Stratton 2001 (58). They studied weight stable HPN patients who had no oral intake and found that 75% experienced hunger, 44% were distressed by the severity of their hunger and 88% had a desire to eat. A few patients regularly chewed, tasted and subsequently spat out food (modified sham feed) in an attempt to relieve distressing appetite symptoms (58). In 2008 Oz et al found that 35 (out of 50) patients were eating normally in addition to HPN, reporting quite good appetite, but not eating what they were partial to. While many patients retained their appetite, 44% could not tolerate “heavy” foods and satiety was reached quickly due to the

feeling of gastric fullness. Nearly half experienced abdominal pain during a meal and 67% report that they did not enjoy food. Oz et al also showed nutritional intake was related to level of work and social activity and related inversely to emotional status. While willing to eat, patients experienced significant side effects which impaired their ability to complete a meal (59).

Oral intake can also depend on the underlying diagnosis. Some patients on PN choose to limit food intake for various reasons including increased pain and diarrhoea (for example in Crohn's disease), rapid transit with a predictable increase in stoma care in patients with short bowel, and a general depressed appetite if receiving nutrients parenterally (60). Patients who can eat without GI discomfort are encouraged to do so if they wish to minimise feelings of social alienation (13). When patients do consume food orally, an intake of less than 10% of basal energy expenditure has been observed (61), or they have been found to consume from 600kcals (52) to1000kcals (13) per day.

Oral intake is beneficial if the side effects are not too great. Oral intake has been associated with fewer metabolic complications (62) and more rapid intestinal adaptation (63).

In paediatrics early initiation of oral feeding allows the infant to learn how to suck and swallow and is the best way to avoid food refusal which often occurs secondary to the absence of sucking during long hospitalisations. In addition oral feeding is more physiological, stimulating gall bladder motility and GI secretion (43).

1.1.7 Intestinal Adaptation

The intestine has an inherent ability to adapt morphologically and functionally following intestinal resection at the physiological, molecular and cellular level (64). The adaptive response in humans has not been well characterised, but increases in the absorption of nutrients have been documented (65-67) in humans following resection. The adaptation of the residual bowel is an important factor in determining whether a patient with a short bowel will progress to permanent intestinal failure and dependence on PN (6).

After massive enterectomy, the intestine hypertrophies and becomes more efficient in nutrient absorption. There is a slight lengthening as well as an increase in both diameter and villus height which effectively increases the absorptive surface leading to enhanced segmental absorption of many nutrients (68-70). Hyperplasia of the mucosa also occurs along with increased mucosal blood flow (6).

Adult Intestinal Adaptation

There is a wide variation in normal adult small bowel lengths ranging from 3-8.5m, with the mean length for women being shorter than that for men (71). Thus the total intestinal length prior to resection will have an impact on the recovery of the patient. If a large percentage of the small bowel is removed, then the degree of small bowel adaptation will need to be greater if enteral autonomy is to be achieved. In adults, resection of 75% or more of small intestine (leaving the patient with 70-100cm of intestine) usually leads to loss of enteral autonomy (72-74). After resection, the presence or absence of a colon in continuity with the remaining small intestine will affect the amount and type of nutritional support required. Generally speaking if the colon is preserved, HPN is likely if <50cm of residual jejunum remain; however with no colon, a longer jejunal length of <75cm will indicate the need for HPN (75).

Clinical evidence suggests that in adult humans, although the majority of spontaneous bowel adaptation takes place during the first 3 months after resection, it can take up to three years or more for adaptation to become fully established (11). From this it can be loosely inferred that if HPN is needed for more than 3 years – it is likely to be permanent. In adults, there is a general consensus that there is reduced likelihood of intestinal adaptation 1-2 years after initial bowel resection (76-78), and the probabilities of weaning from HPN decline substantially after 3 years (79).

Infant Intestinal Adaptation

The subject of pre and post natal bowel growth / adaptation is beyond the scope of this thesis. In children, short bowel syndrome is usually defined anatomically as less than 30% of normal intestinal length or less than 75cm (80). Infant adaptation to full enteral nutrition has been reported with as little as 10cm of residual intestine (81) and indeed, a

high proportion of children receiving HPN make the transition back to enteral feeding in due course (82) if sufficient bowel adaptation occurs. The intestine of the new born and young infant has an enormous potential for re-growth, and given enough time, some patients can achieve sufficient absorptive capacity to sustain growth by enteral feedings alone (83). However often a combination of enteral and parenteral feeding is the most efficacious route to this end (84). Previous research has suggested that infants were likely to require permanent HPN if residual small intestinal length was less than 40cm and the ileocecal valve was absent (32), if there was less than 20 cm residual small bowel remaining (35), if the length of aganglionic bowel is <50cm (43) and if more than 70% of the intestine was resected (33). The most recent evidence suggests that if the remaining jejunoileum is <12cm the ability to wean paediatric patients off PN is small (85). In paediatrics, intestinal adaptation may take as little as 6-8 months or up to 5 years (86).

1.2 Chronic Idiopathic Intestinal Pseudo Obstruction (CIIP)

The term Chronic intestinal pseudo-obstruction (CIP) was first used in 1958 (87). The condition had in fact been described as early as 1896 when 'spastic ileus' was used, cited by Steigmann and Singer (88) and was the subject of an international working team report in 1990 (89). It encompasses a range of rare heterogeneous enteric nerve and muscle disorders (90) which are characterised by a severe impairment of gut propulsive motility with signs and symptoms of intestinal obstruction without evidence of organic causes occluding the intestinal lumen (91;92).

1.2.1 Causes & Symptoms

CIP may be primary (chronic idiopathic intestinal pseudo-obstruction: CIIP) or secondary to connective tissue disorders such as scleroderma, paraneoplasia or to diabetes mellitus. It results from disease involving the enteric neuro-musculature (with characteristics of myopathy, neuropathy, or both) of either one or more segments of the intestine or the entire gastrointestinal tract. The onset of CIIP can occur at any age with varying degrees of symptoms including severe abdominal pain/distension, nausea, vomiting, constipation or diarrhoea, intestinal distension, dysphagia and associated urological problems. Symptoms and signs may be variable in their mix and degree but tend to be intractable,

though the patient may experience good and bad periods over months or years. Pain may frequently require opiate analgesia and the multi-disciplinary approaches of a chronic pain team. Constipation may prove severe enough to justify colectomy, which however often results in ileostomy dysfunction.

1.2.2 Diagnosis

CIIP is distinguished from irritable bowel syndrome, functional bowel disorders or slow transit constipation by combinations of the

- Radiological findings of dilatation of the proximal small bowel
- Manometric results
- Characteristic histological changes
- Inability to maintain normal nutrition

CIIP may require changes in nutritional input to maintain weight and micronutrient intake varying from oral nutritional supplements to home intravenous nutrition (HPN). There are as yet no formally accepted diagnostic terms for "illnesses which fall between pseudo-obstruction and irritable bowel syndrome (93) though for these, the term enteric dysmotility has been proposed (94). Wingate et al (94) regarded abnormal small bowel contractile activity, in combination with episodic or chronic signs mimicking mechanical obstruction of the small bowel, as the defining feature of intestinal pseudo-obstruction, whereas enteric dysmotility was described as abnormal small bowel manometry "without sub-occlusive events".

1.2.3 Management

Management of pseudo-obstruction is largely conservative and focuses on maintenance of optimal nutrition (95). "Pseudo-obstruction" and "systemic sclerosis" combined represented 12.6% of new registrations for home parenteral nutrition (HPN) in the British Artificial Nutrition Survey 2005, the time period closest to patients recruitment to this thesis, 13.7% of the point prevalence of HPN patients. At the Royal London Hospital, the specialist Intestinal Failure (IF) clinic attracts patients who may require a multi-professional approach to artificial nutritional support, and assesses patients for HPN. By

virtue of hospital expertise in intestinal motility and the histopathology of intestinal neuro-musculature, a large number of such patients are referred to the IF clinic. Some require HPN, some do not, but all represent considerable problems of management.

1.3 Parenteral Nutrition (PN)

Today, Parenteral Nutrition (PN) enables us to provide patients with adequate calories, water, nitrogen, electrolytes and vitamins completely independent of a functioning gastrointestinal tract. However the idea of intravenous infusion is not a new concept. For more than 3 centuries, physicians and scientists had dreamed of providing all required nourishment by vein (2).

1.3.1 A Historical Perspective

The first documented reports of intravenous infusions date back over 350 years. In 1616 William Harvey discovered the circulation of blood (96). The first experiments on intravenous injection took place sometime in 1656, in Robert Boyle's quarters in the United Kingdom by Sir Christopher Wren (the architect of St. Paul's Cathedral), who introduced substances including wine, ale and opium into the veins of dogs (97). His intravenous administration apparatus was a goose quill attached to a pig's bladder.

Until the late 19th century this research was followed by a series of experiments into the intravenous infusion of many substances into both animals and humans.

Table 1.1: First Attempts of Intravenous Infusion into Animals and Humans

Year	Researcher	Experiment
1616	William Harvey	Discovery of the circulation of blood (96)
1666	Sir Christopher Wren	IV infusion of wine, ale and opium into dogs (98)
1667	Jean Baptiste Denis	Lamb to human (Louis XIV) blood to blood transfusion (96)
1679	Courten	IV infusion of oil (99)
1818	James Blundell	First man to man blood transfusion (100)
1832	Thomas Latta	Use of IV saline in patients dehydrated due to cholera (101)
1843	Claude Bernard	Infusion of egg white into animals (102)
1873	Hodder	Infusion of milk into humans (103)
1891	Matas	Use of IV saline in treatment of clinical shock (102)
1896	Biedl and Kraus	IV infusion of dextrose into humans (104)

The method of IV administration was not safe or fully accepted until Joseph Lister and Louis Pasteur identified the principles of asepsis (1870) and the implications of microbial infections (1877) respectively (105), and until in 1923 when Siebert brought an understanding and solution to the causes of frequent pyrogenic reactions (106). Even at this stage the improvement of nutritional status was not the main focus of developing the IV technique.

1.3.2 PN - First Attempts

It was not until the early 20th century that the idea of IV infusion being used as an artificial gut started to develop. In 1911 Kaush administered (5% and 10%) IV glucose into man and Yamakawa (1920) started to investigate the IV infusion of fat (caster oil) (107), which caused serious intolerances. Henriques and Anderson demonstrated that normal weight and positive nitrogen balance in a goat could be achieved and maintained with intravenous feeding (1930) (105). Elman, Weiner and their co-workers began to experiment and develop the peripheral infusion of protein hydrolysates and dextrose (108). As late as 1947 Robert Elman repeated his belief that PN was only for short term use, however advances in medicine and surgery (e.g. antibacterial bacteriostatic drugs

and radical intestinal surgery) increased the number of patients who would benefit from more long term support cited by (41).

The first report of successful parenteral nutrition was in a child and was published in 1944 by Helfrick and Abelson (109). This paper was partly republished in another journal in 1978 (110). It describes the case of a 5 month old infant with Hirschsprung's disease who was given intravenous feeding with carbohydrates (50% glucose) and amino acids (10% casein hydrolysate), followed by an homogenised olive oil-lecithin emulsion for 5 days. The child survived and the Hirschsprung's was eventually treated with prostigmine. However these papers are rarely cited.

1.3.3 Evolution of Intravenous Catheters for Nutrition

PN solutions were becoming more advanced and physiologically stable, but it was not until Aubaniac, a French surgeon, perfected the subclavian venipuncture technique (111) that the administration of PN as we know it today started to appear. Stanley Dudrick (and his colleagues) working in Rhoads's laboratory (1968) initially attempted complete intravenous hyperalimentation in dogs (112-114), and it was first successfully demonstrated in 1966 when Dudrick and his co workers devised a method by which a catheter could be implanted and maintained in the superior vena cava for long periods of time (115), allowing physicians to feed higher concentrations of PN (hypertonic), as the glucose and amino acids were being administered into the superior vena cava and immediately diluted with large volumes of blood, preventing injury to the intimal wall of the vessel (116). Thus it became unnecessary to give the very large volumes of PN given previously. They went on to describe the first demonstration in any animal species (almost 100 Beagle puppies) of growth and development with total intravenous feeding (117).

1.3.4 Development of PN Infusions

Between the first successful case of PN in an infant in 1944 (109), and the development of what was thought to be a safe fat emulsion (Intralipid) in 1963 by Edgren and Wretlind

(118), interest in PN was increasing, and there are several publications reporting the use of PN as a viable method of maintaining both human and animal nutritional status (112;119-121).

In these first reports the PN consisted of only nitrogen (protein hydrolysate) to attain nitrogen balance, large amounts of dextrose (protein sparing), in a volume of approximately 3 litres (maximum volume tolerated). The protein and the glucose had to be sufficiently diluted for peripheral vein administration to ensure the solution had a low enough osmotic load to prevent thrombophlebitis. However this combination did not provide enough calories to sustain patients over long periods. Rhoads pioneered the approach of feeding large volumes of PN (5-7 litres) simultaneously with high strength diuretics (122). Further research by Dudrick suggested that positive nitrogen balance could not be achieved unless 150 Kcals per gram of nitrogen was provided (123). Hydrolysates of casein and of beef-blood fibrin were the primary sources of amino acids in PN into the early 1970s (41). The first commercially available amino acid solution was Freamine, which had the amino acids as chloride salts (124).

In 1968 Wilmore and Dudrick went on to report what they term “the first clinical application of TPN”(2), where a newborn infant with multiple congenital GI anomalies (massive atresia of the small bowel) was referred to Dudrick to try his “puppy feeding” method. She was fed entirely by vein for 45 days and, thereafter primarily by intravenous hyperalimentation for 22 months (125). After 6 months of intravenous feeding they estimated that 97% of all the nutrients she’d had during her entire life were by vein. She represented the first human demonstration that one could give enough prolonged nutrition by vein to grow, and that tissue synthesis could be achieved when nutrients are provided exclusively by vein. In 1969 Dudrick et al reported methods and results of total intravenous feeding used as the sole means of nutritional support for prolonged periods of time in adults (over 300) and children with severe GI disability (126). They report normal growth and development of 12 newborn infants fed intravenously for 7-400 days.

In 1969, Filler et al (127) reported survival of 14 infants under 2 months of age who were fed an intravenous fat free solution via a central venous catheter for 14 – 60 days. All infants survived and were discharged well. They note that this method of feeding reduced the length of hospital stay and improved the clinical status of the infant during the preoperative and convalescent periods. The patients who were fed intravenously had weight gain comparable to that of healthy well nourished infants. In those with sepsis and increased metabolic requirements, nutrients available for growth were reduced – which was reflected in a flatter growth curve. Two of the infant's non-specific chronic diarrhoea was resolved completely as a result of complete bowel rest for an extended period.

There are a series of reports that focus on PN being used as a temporary therapy, and provide a lot of details regarding clinical parameters such as growth charts, albumin/nutritional status and disease remission. In children growth can be used as a proxy for overall nutritional status (82). This was followed by (mainly anecdotal) reports of the use of parenteral nutrition for the reversal of growth arrest in adolescents with active Crohn's disease (128;129). At this time the controversial question of how best to manage these patients was being addressed, with resection of diseased bowel, or by reversing nutritional inadequacy either via the enteral or parenteral route? (130)

This is followed by numerous reports of successful parenteral feeding in children (23;127;128;131;132). From this point on PN is considered a clinical reality and many reports of prolonged PN can be found in the literature.

1.3.5 Lipids

The history of fat emulsions is chequered with episodes of haemorrhage, toxicity and coagulation problems (133). The first generation of parenteral fat emulsions used various emulsifiers, including egg lecithin in the late 1920s. After severe side effects had been reported, the emulsion was withdrawn by the end of the 1930s (134).
The second generation of parenteral fat emulsions contained purified soya lecithin in combination with a synthetic emulsifier and the oil phase used consisted of cottonseed oil. Again, pharmacological issues necessitated development of a new formula, since

long-term administration of cottonseed-emulsions led to toxic side effects owing to gossypol contamination (135).The introduction of Intralipid® in the early 1960s (136) marked the third generation, and many emulsions with similar compositions (soybean oil, egg lecithin) have since been introduced. Initially it was reported to be used with caution in neonates (137), but as soybean lecithin was reported to be more toxic than egg lecithin, this is now not used in commercial products, and glycerol is the only isotonicity agent.

In the late 1980s a new approach was made in the oil phase, using a combination of medium-chain triglycerides (MCT) derived from coconut oil and possessing C8-10 chains, together with conventional long-chain triglycerides (LCT). Eckart et al. (138) and Guisard and Debry (139) claimed MCT to have the advantage over LCT by providing better availability, owing to faster metabolisation and faster clearing and also from a metabolic and immunologic point of view. This resulted in development of synthetic Sructured Lipids (SL) in the early 1990's, an example of which being Structolipid (Fresenius-Kabi). These SLs are made by hydrolysis of Soyabean Oil and MCTs with subsequent random reesterification of MCFAs and LCFAs. The advantages of structolipid include improved liver tolerance, controlled plasma concentration of triglycerides and improved protein economy (140).

More recently advances of the use of fish oil in parenteral lipid emulsions have been explored. Parenteral Fish Oil is a novel emulsion available in a ready-for-use form, compounding soybean oil, medium-chain triglycerides, olive and fish oil (SMOF) (141). This so-called SMOFlipid (Fresenius-Kabi) is a 20% lipid emulsion with the lipid being a mix of 30% MCT, 30% Soyabean Oil, 25% Olive Oil, and 15% Fish Oil (142). A 2004 study reported that a short infusion of SMOF in healthy male volunteers, when compared with pure SoyabeanOil (Lipovenoes; Fresenius-Kabi), was well tolerated and increased plasma elimination, as evidenced by a less marked increase in serum triacylglycerol concentration at the end of infusion and lower serum triacylglycerol concentrations (143), although there is very little evidence for the use of SMOF in HPN.

The advantages of using lipid emulsions are that they are isotonic, so are suitable for peripheral infusion, they allow greater provision of nutrients in a smaller volume and are considered protein sparing (144). Dextrose solutions are more likely to lead to thrombosis than a lipid mix (145;146). Choline is required to transport fat in the liver to peripheral fat stores. Choline is synthesised from ethanolamine by transmethylation of a methyl group from the amino acid methionine. This amino acid is in high concentration in the crystalline amino acids usually added to TPN solutions (116). Although lipids are essential in PN solutions, they are toxic, in the accumulation of the non oxidised fraction in the reticuloendothelial system of the liver and in peroxidation by essential fatty acids (4;147).

1.3.6 The Evolution of Modern PN

The basic principles leading to the success of parenteral nutrition were 1) the provision of all nutrients available in intravenous form, 2) concentrated in a fluid volume equal to normal daily water requirements, 3) infused into a high flow central vein, 4) at a constant rate over 24 hour period to permit maximum utilisation and renal excretion (148). In both adults and paediatrics, the infusion of a hypertonic nutrient mixture at a constant rate into an area of rapid blood flow circumvented problems previously encountered in patients when hypertonic mixtures were infused into peripheral veins (149).

By the early 1970s PN had established itself as an important therapy. On both sides of the Atlantic, PN was being administered using separate bottles and bags to which further additions were frequently made by medical or nursing staff (150). It was not possible to purchase PN fluids in a complete form, as there were many problems with stability and shelf life. This meant that PN was administered as a sequential single bottle regimen, or as a multi bottle regimen using Y or W connectors. Then in 1974, Solassol and Joyeux from Montpellier introduced the concept of “melange nutritive” utilising a reusable silicone bag into which all the nutrients were mixed and infused over 24 hours (151). Pharmacy compounding of all in one PN solutions was then started in France by Solassol & Joyeux (152), in Canada by Jeejeebhoy and in the UK by Powell-Tuck and his colleagues who developed a sterile disposable 3L PVC bag to enable infusion of feeds

compounded by pharmacists under lamina flow conditions. In 1977 this ambulatory system allowed the first UK patients to go home from St. Marks hospital (153).

1.3.7 Early Clinical Administration of PN

Initially parenteral nutrition was administered in the inpatient setting for set periods of time of between 25 – 50 days (154) and provided the fluid, electrolytes and minimal calories to support life (2). The nutrient solution was delivered by gravity drip in adults and by peristaltic pump with variable speed control (enabling delivery at a constant rate) in paediatrics. The nutrient solution consisted of glucose, fibrin hydrolysate, minerals, vitamins and trace elements, and did not contain any lipid as safe intravenous fat emulsions were unavailable at that time. It was administered over 24 hours to achieve maximum metabolic efficiency and assimilation of the nutrients (126). It was becoming clear that tissue synthesis, weight gain, growth and development could be achieved by intravenous administration of basic nutrients.

This led to a tailoring of specific PN regimens to the patient and the disorder (126). Community hospitals were also being encouraged to embark on PN programs (155). Ambulatory HPN was a logical and obvious outpatient extension of the clinical application of intravenous hyperalimentation in hospitalised patients (156) as parenteral nutrition proved both expensive and psychologically disabling to the patient.

By the early 1970s indications for PN had extended from patients with severe alimentary disorders to a host of debilitating illnesses whose metabolic demands often exceed the capacity of the normal alimentary route (157).

1.4 Home Parenteral Nutrition (HPN) – First efforts

When TPN was first introduced, it was thought that it could only be performed in the hospital under the strictest aseptic procedures. As experience with the technique was gained and the procedures simplified, parenteral nutrition become widely used, both in small community hospitals and tertiary medical centres (158). The introduction of TPN at home was a logical extension, it was used almost exclusively in relatively stable patients

with extreme short bowel (36;159-162). Technical developments in feeding together with the growth of support structures in the community led to a steady increase in the number of paediatric (82) and adult patients receiving HPN.

Shils (41) states the first reported case of HPN was in December 1969 (163), however Dudrick claims he was the first to report an adult patient fed at home entirely by vein. She was a 36 year old woman with widespread metastatic ovarian carcinoma, who was discharged from the Hospital of the University of Pennsylvania in 1968 (2). The capability for providing long term PN out of the hospital was pioneered by Dr. Belding Scribner at the University of Washington (124)

The first mention of paediatric HPN in the literature was in the form of a short abstract by Scribner and Riella in 1975 who report successfully feeding 3 children by TPN at home (164). The general criteria for instituting paediatric HPN was the inability to maintain fluid and nutritional balance on a therapeutic diet or elemental formula and a need for 30 days or more conventional inpatient TPN (165).

1.4.1 Development of HPN

The first report of HPN was by Scribner in 1970 (158), in which he describes the concept of an artificial gut providing prolonged nutritional support. This paper was later criticised as being premature by Scribner and Cole in 1978 (166). The system, which they earlier described, worked well in uraemic patients, but the arterio-venous shunts were clotting when used in malnourished patients due to poor quality veins and abnormal clotting parameters. They then tried a new technique by inserting a stiff Tenckhoff catheter via the subclavian route into the right atrium. However this resulted in mechanical trauma to the superior vena cava causing thrombosis, obstruction and failure of the catheter. In 1973 Broviac (167) reported experience with a soft silicone (Silastic) rubber right atrial catheter which was flexible, inert and anti-thrombogenic. Local and generalised infection was reported as the main complication with a mean catheter life of 144 days. Dacron felt (a type of polyester (168)) placed subcutaneously was shown to promote tissue

fibroblastic in-growth, prevent accidental dislodgement and to and fro motion, as well as obliterating the continuity of the sinus tract between the exit site and vein, thereby forming an anatomic barrier to organisms ascending along the outer aspect of the catheter (167). Silastic catheters have a long life due to their absence of corrosion and their inert behaviour in tissues (169). The ensuing successful long-term venous access resulted in the Tenckhoff catheters being replaced by the Broviac catheters.

Initially the gravity system of infusion overnight was used, but this was found to be unreliable and required constant vigilance. A powered portable device contained in a specially designed vest (2) was developed by Dudrick which eliminated this problem although some of the patients criticised the device as being cumbersome (170). Shils then developed a standard portable pump system equipped with infusion rate monitors which allowed cyclical night time infusion (usually over 10-14 hours) (171). The safe administration of feed during the night gave patients freedom during the day.

Initially lipid infusions were still given separately as they could not pass through the filters. Half of the energy requirements were provided by the lipid infusion.

Cases of intestinal failure which were previously fatale became manageable and HPN technology diffused to Europe from the USA in the late 1970s (170). In 1973 Jeejeebhoy reported total parenteral nutrition at home for 23 months, without complication (161) which was followed by further favourable reports of adult and paediatric HPN (160;171-174). The first patients discharged home on HPN in the UK were at St Mark's Hospital , London and Hope Hospital, Salford in 1978 (175).

1.4.2 Benefits of HPN Compared to Hospital TPN

Generally there were several benefits observed by providing PN in the home.

In adults lower sepsis rates (and thus morbidity) were reported due to reduced exposure to nosocomial flora by being out of the hospital environment, being on a cycled infusion, and being nutritionally rehabilitated with restored immunocompetence (176). Patients'

activities tend to increase as number of hospitalisations decrease (36), improving the likelihood of social rehabilitation.

In paediatrics, resultant hospitalisation due to the necessity of long term nutritional support is both expensive and psychologically disabling (177).The negative side effects of prolonged hospitalisation are well established, including impairment of social and intellectual development in children. So along with the achievement of normal skeletal growth, weight gain and improved states of general well being, HPN offered an acceptable solution to the resolution of social and psychological developmental issues upon return home (36;177-179).

In 1980 Cannon et al were the first group to look at HPN during the first 2 years of life (180). Up to this point, there had been no prospective studies which looked at infants who were raised from the neonatal or early newborn period solely on HPN. They used the Gesell score to determine neurological development, and found that those infants who remained hospitalised or were at home less than 2 months at the time of the test scored lowest in gross motor, adaptive and language skills compared with children who had been discharged for >2 months. At dinner time the children sat with the family for social purposes but showed a persistent disinterest in food. They concluded that if infants were neurologically normal, appropriate developmental milestones could be expected during the first 2 years of HPN. The single most important factor contributing to the normalisation of neurological development was probably the home environment. It was too early to tell if the HPN child would exhibit normal intellectual function in school. They concluded that HPN in infants promoted normal physical growth and development during the first 2 years of life.

HPN emerged as a life saving nutritional therapy which permitted patients ranging in age from 1 – 72 years old to resume normal lives at home (2), and the ability of the patients to learn the aseptic technique within a few weeks with daily training sessions was also noted (171).

1.5 Current Techniques of HPN

1.5.1 Administration of HPN

HPN can be total or partial, permanent or temporary (181). Today parenteral nutrition is administered either peripherally or centrally. Peripheral catheters are appropriate for short term PN and are usually used to feed low osmotic load PN solutions. Therefore it is unusual to see them used in HPN patients who require long term (often life long) nutritional support.

Central Venous Catheters (CVCs) are used for longer-term administration of PN and are inserted by a radiologist. The catheter tip should lie above the junction of the superior vena cava and right atrium, correct placement and absence of insertion related complications (vessel puncture and pneumothorax) should be confirmed by X-ray. Peripherally Inserted Central Catheters (PICC lines) are occasionally also used. There is a range of central catheters available which include catheters with single or multi-lumen. In Europe portacatheters are widely used (Dr. J. Shaffer, personal communication 23rd July 2010). The clinical picture and the clinician's personal preference dictate choice of catheter.

In the UK intravenous nutrition is administered through a volumetric pump with occlusion and air-in-line alarms to minimise infusion complications. Specifically in paediatrics, other pump requirements have been reported to be: simplicity of priming the set and clearing entrapped air, the pre-selection of infusion rates, a minimum number of false alarms and motor noise, light weight and a carry handle (182). However there is a variability in the administration of PN, for example pumps are not routinely used in Poland (J. Shaffer, personal communication 23 July 2010), and the parents of children on HPN have been reported to compound the HPN mixtures in their homes (183).

In an acute setting PN will usually be administered over a 12- 24-hour period, however this would not be appropriate for patients at home. Generally patients infuse over a limited period (cyclic PN) – frequently approximately 12 hours over night, three to seven nights per week. The goal of cyclic PN is to infuse the nutrients that the patient requires

in a shorter time period - the proposed advantages being the physiological benefit of mimicking the fasting and fed states and the psychosocial benefit of giving the patient "time off" from the infusion for normal activities of daily living (184). Cyclic PN appears to be as effective as continuous PN in maintaining nutritional status (185;186), potential advantages of cyclic infusion include improved insulin levels, reversal of hepatic steatosis and liver enzyme changes associated with continuous infusion (186). Interrupting PN infusion allows the body to convert to the oxidation of fat as opposed to the oxidation of carbohydrate that dominates during continuous PN, promoting mobilisation of lipid, transport of fat out of the liver and positive nitrogen balance with decreased lipid storage (187). It is important to get the correct regime to allow the patient a sufficient amount of time disconnected from the pump to lead an independent existence, whilst providing the patient with adequate nutrients. So there can be some degree of flexibility to allow for social and recreational needs (13).

1.5.2 Content of HPN

PN solutions bags are mostly compounded in a commercial pharmacy 90% or hospital pharmacy 10% (2001 BANS Data), and then delivered to patients in their own home. Special arrangements must be made to store the PN bags, as it is customary for patients to have on average two weeks supply at any one time. PN bags are frequently refrigerated as this better maintains the stability of its macro and micronutrients and helps to prevent bacterial growth – as PN solution is an excellent culture medium for most aerobic bacterial pathogens and all Candida pathogens (188). Off the shelf bags (PN bags which require the addition of vitamins and trace elements) often are, but do not have to be stored in a refrigerator.

The content of the feeding bags is tailored to individual patient needs, and range from simple intravenous fluids to entire nutrient requirements including protein, carbohydrates, fats, minerals and trace elements. The energy in PN bags is described as non-protein calories.

1.5.3 Nitrogen / Protein

Nitrogen is usually supplied as a balanced mixture of crystalline amino acids, or dipeptides for the more labile amino acids e.g. glutamine. Different amino acid profile solutions are available for particular disease states. Most patients can be maintained with 0.16 - 0.2 g N/kg body weight/day but should not exceed 0.3 g N/kg body weight per day. The optimum amino acid profile for PN reflects known requirements of essential amino acids. The ratio of essential amino acids: total nitrogen should be 1:3. Some amino acids may be conditionally essential or may be necessary to improve the utilisation of others.

1.5.4 Lipid

Lipid serves two purposes in parenteral nutrition – as a source of calories, and as a source of essential fatty acids (EFA) to prevent EFA deficiency. Excess lipid has been demonstrated to result in hepatic complications, but the optimal dose and type of parenteral lipid that should be provided to minimise hepatic dysfunction remains unclear (189). The lipid content of HPN is very variable and reflects the energy needs of the individual and the extent to which essential fatty acids can be absorbed enterally (190). US guidelines suggest that fat should provide 20 – 30% of energy needs in PN (10) commonly in the form of long-chain triglycerides and essential fatty acids which are needed to maintain cell membrane integrity and immune function. In clinical practice many centres use relatively low parenteral lipid regimes in order to ensure the provision of EFAs and minimise the risk of hepatic complications associated with HPN. The use of SMOF, Structolipid and ClinOleic in preference to Intralipid (100%LCT) is slightly increasing in clinical practice, as there is some evidence that 100% LCT emulsions can cause physiologic and metabolic problems. Addition of lipid increases the cost of PN, but the clinical benefits of reducing high glucose loads and hypertonic feed may offset this cost. Lipid emulsion is the most unstable constituent of an all in one bag. Stability is primarily affected by pH, amino acid composition and electrolyte content.

1.5.5 Carbohydrate

Carbohydrate is added in the form of glucose, which is a cheap energy source. There is a stated maximum rate of glucose oxidation (about 4-7mg/kg/min), and although exceeding this can increase the risk of complications such as increased CO_2 production, fatty liver secondary to hypertriglyceridaemia and hyperinsulinaemia, many HPN patients will tolerate higher glucose infusion rates during cyclical PN. A study by Williams et al (191) demonstrated no elevation in plasma HbA_{1c} levels in a group of patients receiving glucose based solutions (median infusion rate 11.8mg/kg/min) for HPN. It is thought that there is some degree of adaptation to glucose infusion rates during prolonged glucose infusion, resulting in an increased capacity to oxidise glucose (192).

1.5.6 Electrolytes

Electrolyte content of the PN bag is altered according to serum measurements, fistula and stoma losses and must be checked at outpatient visits.

1.5.7 Vitamins

The American Medical Association provide guidelines that suggest water soluble vitamins exceed normal daily requirements in order to offset tissue losses and facilitate the synthesis of new tissue. Fat soluble vitamin requirements are often dependant on the number of fat versus fat free bags given per week.

1.5.8 Trace Elements and Minerals

In enteral nutrition the GI tract selectively absorbs the amount of trace elements required. PN bypasses this mechanism and the risk of over dosage is increased. The needs of most patients can be met by standard trace element solutions devised for PN, however, micronutrient requirements for parenteral nutrition (PN) are not well understood and guidelines for supplementation are outdated (193).

1.5.9 Complications

The main complications of PN can be divided into metabolic, physiologic, mechanical or infectious.

Table 1.2: Complications of Parenteral Nutrition

Type of Complication	Example of complication
Metabolic	Fluid overload, hyperglycaemia and electrolyte abnormalities
Physiologic	Rise in serum bilirubin, fatty liver, choleliathiasis, and cholestasis
Mechanical	Catheter related thrombus occlusion or fracture. Insertion related pneumothorax, chylothorax, air embolism, cardiac arrhythmias or nerve injury
Infectious	May be secondary to catheter or other concurrent infection

Many non specialist centres are not used to dealing with HPN related complications and it is therefore most important that the patient or carer be adequately trained to recognise and react appropriately to serious symptoms which often requires contacting or returning to the HPN centre – which may be many miles from the patients home. The nutritional requirements of the patient remain the clinical responsibility of the hospital that has arranged the HPN service.

Many patients report that at least some of the equipment was primarily designed for hospital rather than home use. Therefore a patients' organisation PINNT has devised its own stand to hold the feed pump. It has found increasing use in the UK (194).

1.5.10 Multidisciplinary Team (MDT) Approach to Care

Both adult and paediatric centres have recognised the importance of a MDT approach to care (124;149;195). Reduced rates of catheter sepsis were noted to be directly related to the formation of nutritional support teams. Specialist centres providing HPN will have a team of clinicians, surgeons, anaesthetists, intensivists, radiologists, clinical nutritionists, specialist nurses, pharmacists, dietitians, biochemists and social workers. The conditions

which lead to intestinal failure are often associated with disabilities such as high output stomas, profuse diarrhoea, abdominal distension, vomiting and pain. Patients therefore potentially have a lot to cope with in addition to the invasive provision of PN, thus the support of a good team is essential for success. An ongoing team effort can yield benefits of continuity, cohesiveness, mutual frame of reference and development of a skill peculiar to HPN care and management (13).

Training is often provided to patients (or carers) whilst they are inpatients, which requires a substantial dedicated training programme for the maintenance and care of CVCs. Specialist nurses and MDTs need to undertake and assess training. The patient, carers and GP must be provided with education material. Most minor problems are handled by telephone calls (60), and if adjustments to the HPN infusion are needed, the local carer can contact the HPN centre by phone.

Industry has already changed its service system from one which predominantly dealt with delivery to a more complete service (194). Commercial home care companies started to assume much of the care, supply and oversight responsibilities of HPN (41). In 2003 it was estimated that PN was supplied by commercial homecare companies in 89% of cases in the UK (175). Some companies provide telephone support and now telemedicine. Centres who do not use commercial homecare companies to provide community support offer a less than optimal service (175).

1.6 HPN Training

It can not be denied that discharge from hospital is vital to the rehabilitation of patients with intestinal failure, markedly improving their self image and the desire to participate in their own personal care (179). However, extensive training is required for both patients and the parents of a child on HPN (196), and in many ways patients (and or their carers) have to learn a professional clinical skill (197). Users must become technology friendly for the technology to fulfil its role and it must be recognised that technology is always both enabling and constraining (198).

In paediatric centres, training is generally reported to take between 2 -5 weeks in the inpatient setting, sometimes parents or carers are required to be resident in the hospital (199) or nearby hotel if the patients home is many miles from the training centre (159) and in one centre a nurse from the unit went home with them for 1 or 2 nights (200). Written guidelines for handling CVCs are also given to patients (201). This can be an extremely stressful period and families who are anxious should be encouraged to cope with their needs before hospital discharge so that they can feel and be perceived as competent carers (202).

In adult centres the length of training varies from between 2-6 weeks. At the Royal London Hospital, patients are often sent home for their training. The patient/carer is initially taught basic aseptic technique and how to disconnect from the equipment so they know what to do if anything goes wrong in the night. A company nurse then will go to the patient's home to aid the set up and disconnection of the HPN for 3 months. The nurse is responsible for gradually teaching the patient/carer the whole process. This enables much earlier discharge of the patient.

Both adult and paediatric training programs include observation to familiarise the patients or carers with the technique, repeated interviews, active training in aseptic techniques and equipment handling for connection, disconnection and simulation of the home situation in an isolation room.

Adult and paediatric literature agree that training should be given to other members of the family so there is a back up, alternative caregivers can also allow the main carer to take time off from the demands of daily HPN administration (12;203;204). However this is not always possible and in one paediatric study only 25% of the families could rely on someone else to connect or disconnect the HPN (205). In 1998 the Carers National Association estimated that in the UK, around 850,000 carers provide a range of care for more than 50 hours per week and 60% of carers receive no regular support services (206). BANS has drawn attention to the need to provide care for the carers (194). In carers of a child on HPN, distress may be alleviated by paid help, but those who can provide direct

care (e.g. registered nurses who can offer respite from a patient's medical care demands) are more effective at decreasing stress levels (207) and sometimes considered essential (182).

Points taught to patients or carers before discharge include:

- Hand washing technique
- Principles of asepsis
- Catheter care
- Infusion
- Care of parenteral nutrients
- Care of infusion pump
- Monitoring at home
- Problem solving
- Emergency contacts

Homecare involves more than simply transferring a particular technology from the hospital to the home – it requires transferring knowledge and skills to lay people and making sure that the home and social environment enable a safe, effective, appropriate and personally satisfying use of technology, otherwise ineffective potentially hazardous and socially compromising treatments may be disseminated (208). Typically health professionals emphasise infection prevention more than managing depression or other problems (209). MDT staff should be sensitive to the psychological as well as technological needs of HPN patients (210).

1.6.1 Adult HPN Patients and Family Support

Typically adult patients are encouraged to care for their own HPN administration if possible. However, family support can be important, and carers should be included in the teaching programme if willing and able. If self care is not viable, given careful training, an intelligent lay person can look after a patient as long as adequate community nursing support is available, but physical and mental strain while carrying out care has been reported (211). It is not uncommon for both the patient and spouse in the family to

experience fear, anger and depression resulting in marked changes in family life (37). The transition from hospital to home may be smoother if the patient has another patient contact who has previously undergone the same process (10). Patients have stated that they would like to have a means of communicating with other individuals who also receive HPN (210).

1.6.2 Caring for an Adult on HPN

Caregiving effectiveness is defined as the provision of technical, physical and emotional care that results in outcomes of optimal patient Quality of Life (QoL) and physical condition, minimal technological side effects for the patient, and the maintenance of the caregivers health and QoL (212). Caregivers of HPN patients must have some knowledge of technical nursing care, of the organisation and delivery of the HPN supply, and are required to make judgements about the day to day impact of the treatment. This can be extremely stressful and major depressive disorders (situation depression) have been observed (212). A distressed, anxious caregiver has a deleterious effect on patient condition. A link between negative care giver – care receiver interactions and patient complications has been observed, while positive interactions have been associated with increased compliance and QoL (213).

1.6.3 Caring for a Child on HPN

Paediatric HPN patients and their families benefit psychologically by being at home and resuming relatively normal lives (177), and although the benefit of bringing their child home can not be underestimated, they are accepting a huge responsibility by becoming both parents and medical providers (207). Along with the task of mastering the technique of HPN, parents and their families potentially cope with multiple setbacks, extensive hospitalisations and re-operations (83).

Parents function as gatekeepers of their children's health (214), often becoming responsible for many of the highly skilled nursing care tasks (207). When commencing HPN, parents need to make a physical and emotional commitment if the therapy is to be

successful (179) and perhaps the most difficult factor to assess pertains to the time, effort and dedication required by these parents (83). The majority of parents tend to be highly motivated but daunted by the prospects of having to take on their child's total nursing care (203). Parents have been shown to provide a high quality of HPN care (16). Thorn highlights that home management of a gastrostomy and its physical and social complications require an intensive effort, high level problem solving and constant adaptation (215), and parents of children on HPN must face similar problems by becoming experts in the technical care of their child (202).

Caring for a young child on HPN differs from an adult caring for themselves or being cared for. Babies and young children will want to pay with, pull at and chew on the catheter and tubing if it is within reach (216). Parents are advised to coil and tape catheters close to the body at all times and should try to limit active play during HPN infusion by making it a special time for quiet play. Once the child is home the family is faced with integrating these procedures into the family lifestyle (204) .

Carers are aware that the survival of their child is dependant on their skill in delivering the HPN (217), and many find this a great burden (199). In one study the authors state that sepsis related deaths of a 1/3 of the children could have been prevented had the parents followed instructions and brought the child into hospital when fever developed (31). This burden is further illustrated in 4 reports in which psychological investigation showed that all parents had behaviour disorders (depression) strongly related to the knowledge that their child was dependant on HPN for an indefinite period (218), 77% of parents exceeded the threshold for psychiatric morbidity (219), over 60% of families experienced deterioration in their family life i.e. social life activities and overall QoL after their child started HPN (202) and over 50% of parents abstained from alcohol (205). A child's illness can have a negative effect on the parents' marriage and result in the experience of marital distress (220).

The first group to identify problems caused to the carers of a child on HPN was Byrne et al. In their series of 6 children treated on the HPN programme, a mother elected to

discontinue the HPN as she felt unmotivated and received little support from her husband and family. She felt depressed by the prospect that the HPN would be required indefinitely and chose to feed the child orally. The child did poorly from a nutritional standpoint, but the authors do not state if the child survived (165). Despite the growing numbers of families involved in HPN, little attention has been given to the effect of caring for their child on the parents (202). A study which looked at the parents caring for children with pseudo-obstruction (38% of the children were on HPN) found that these parents had poorer emotional status, were less resilient emotionally and that the child's mental health and self care/mobility were strong predictors of the parent's emotional status (90).

Parents with a medically fragile child may be at a greater risk of psychological distress, however quantitative research specifically on this group of patients is minimal, Leonard et al found high numbers of parents (over half of the mothers and fathers) caring for a medically fragile child reported symptoms high enough to merit psychiatric intervention. Overall both parents distress levels were affected by increased family responsibilities (207).

There are many sources of stress reported (221) including

- General uncertainty about the child's future
- The unpredictability of hazardous events that may occur
- The need to balance domestic and employment responsibility
- Physical exhaustion associated with sleepless nights/sleep disturbance

Much of the success of homecare depends on the parent's psychological status (207) this has lead authors to advocate parental support (82;215) of an informational, instrumental and emotional nature (202). Family members should be encouraged to talk about their feelings with someone who can assist them in dealing with these emotions. Such assistance may come from a social worker, support group, close friend, family counsellor or clergy person. This support is vital as parents with higher rates of psychologic stress may be less able to nurture their children (222). Unfortunately many find that when they

seek support from support agencies there is no understanding of the medical problems of the child or the social or emotional needs of the parents (199).

Parents frequently feel trapped by the needs of the child (199), suffer with social isolation and feel as if they lose some control over their child's care to the healthcare team (202). Networking with other parents often provides one of the best resources to reduce feelings of isolation (204). Engstrom et al showed that social integration of the parents is high, whereas attachment which deals with deeper, emotional relations is affected. The authors postulate that families are in contact with more people than usual because of the complex medical situation but the level of the contact is superficial, allowing less time for deeper relationships with relatives and friends (205).

A recurring theme in the literature is the question of candidacy of single parent families. Some centres feel that the main carer must be in a stable relationship (199) , while others felt single parent families were not a contraindication for HPN (223) provided that social help and home nursing assistance were organised (224). There is general evidence to suggest that parents who do not share parenting with another adult experience the psychologic strain of making decisions of potential lifelong consequences alone and they lack time to carry out household and child rearing tasks (222). Also married subjects tended to have moderately lower levels of depression and anxiety than those who were not married (220).

There are a variety of reasons some parents may not able to administer HPN including the technical and emotional demands (199), inadequate home situations (83) and disruption of families secondary to marital disharmony (225).

There are very few reports in the literature of grandparents providing total care (223). Younger parents (younger than 30 years) had significantly greater psychosocial adjustment difficulties (220).

1.6.4 Maternal Burden

Although HPN represents a challenge for the whole family (204), the mother is usually the parent responsible for administering HPN (31;226;227). A study by Thyen & Perrin reported that one third of mothers quit employment to take care of a technology dependant child (defined as children with 'a medical device to compensate for the loss of a vital bodily function and substantial and ongoing nursing care to avert death or further disability' (228)), and that mothers still carry the major burden of child health care (82% attributing their non employed status to limitations arising from the disability of their child). Those who remained employed reported significant work related problems including having to work fewer hours, to take time off, to change jobs to accommodate care at home or to remain at jobs because they feared the loss of health insurance (229). In society, mothers of chronically ill children have a more intense involvement with the sick child whilst ensuring the well being of all family members, and fathers have more concerns about competing obligations between work and family (230). In a recent study of families with a child on HPN, mothers QoL scores were lower than the normal population, and lower than the father's scores for items related to work, inner life and freedom. This group also found that maternal anxiety was associated with fear of being judged and culpability (231). In 1999 Thyen et al found that employment acted as a protective factor when caring for a chronically sick child, with relatively higher levels of psychological well being reported than those who were unemployed (229).

1.6.5 Caring for a Chronically Sick Child at Home

HPN is an intricate procedure and the ability of the carers to provide this complex care is an issue. Reported ideal candidacy for HPN training includes motivation, intelligence, previous para-medical training (232), minimal/adequate housing conditions (bathroom facilities, telephone), ability to understand the basic rules of asepsis (200), psychological stability (202) and having a reliable home environment (227).

The health and well being of children are inextricably linked to their parents' physical, emotional and social health, social circumstances and child rearing practices (222). Parenteral adjustment in terms of psychological distress, marital distress and family

functioning caused by caring for a chronically sick child are well described (220). Parents' mental health affects their individual functioning; social relationships with their spouses, partners, co-workers, and other adults, and their child rearing behaviours (222). Parents with a medically complex child at home report satisfaction in relation to witnessing the emotional and social growth of their child (233;234), but caring for such a child can result in adverse health impacts on the primary caregivers (228).

Recent research has shown that parents caring for children with other chronic illnesses have an increased risk of stress:

Cancer - Parents experience feelings of loneliness and uncertainty, post traumatic stress symptoms, fear of relapses, worries about infertility and uncertainties about the future. Although family functioning is satisfactory and consistent over time (220), higher levels of stress are associated with lower levels of family cohesion (235). Social support and family relationships have shown to significantly influence parental adjustment in a number of studies (236-238). Escape avoidance, mainly through wishful thinking, is used to a great extent by parents of children with cancer and to an even greater extent by parents of children infected with HIV (239).

Autism - Parents with a child with autism tend to use coping behaviours of distancing and escape, a behaviour aimed at withdrawal from a stressful situation. Seeking social support from within the family's social network is a large part of the external family coping strategies (240).

Type 1 Diabetes – Parents of a child with type 1 diabetes tend to use planful problem solving, positive reappraisal and seek social support. Parents must deal with the risk of severe insulin reactions, current and future medical complications, repeated hospitalisations and the fact that the child's lifespan may be reduced (241).

Cystic Fibrosis - Parents HRQoL is not affected by the severity of the cystic fibrosis. The importance for parents to be able to express their emotions and call on social support has been reported (242).

1.7 Epidemiology of HPN in the UK

Data on the number of patients treated by HPN in the UK has been collected since the early 1970s. In 1977 it was decided that, because individual centres in the UK were unlikely to accumulate a large experience of this type of treatment, that a national register of cases should be established. Data were recorded on the University of Manchester /MRC computer at Hope Hospital (243). The British Artificial Nutrition Survey (BANS) has been officially recording this information since 1995 and all providers should be supplying data to this register on a regular basis. Each annual report has been highlighting increasing numbers of HPN patients.

The majority of adult patients are treated in one of two NCG (National Commissioning Group) funded Intestinal Failure (IF) centres: Hope Hospital and Saint Marks Hospital IF services were designated from 1 April 1998. However BANS data has identified up to 50 adult centres with experience of providing HPN at one time or another, only 20 – 25 of these centres having regular experience. Many of these other centres are already working closely with the two national IF centres whose services can be saturated for long periods of time.

Paediatric small bowel transplantation is currently commissioned with Birmingham Children's Hospital and King's College Hospital in the UK, but the current contract does not include the management of those children with complex intestinal failure in whom small bowel transplantation may not be necessary. Therefore intestinal failure services for children are managed regionally, with approximately 10 centres demonstrating a degree of expertise.

1.7.1 Adult Prevalence of HPN

In 2001 BANS estimated that in the UK at any one time approximately 500 patients were being treated by HPN, but this could have been as high as 700 allowing for underreporting. This 40% inaccuracy in the recorded data may seem large, but was probably due to a large number of services treating small numbers of patients (sometimes for long periods) and failing to report. However by 2007 this figure had increased to 870 (period prevalence). The continued collaboration between HPN provision providers and BANS to try to obtain accurate numbers means that the current BANS HPN data accounts for approximately 91% of all known HPN patients.

BANS publish an annual report which includes detailed information on HPN in the UK. The latest 2008 report can be found at the following URL:
http://www.bapen.org.uk/pdfs/bans_reports/bans_report_08.pdf.
The BANS data that is most relevant to the subjects in this thesis is the 2001 report.

In 2001 there were 120 new adult HPN registrations; however the total number of patients treated by HPN tends not to rise so quickly because of either death or cessation of therapy. There are 3 broad categories of patient

- Those for whom it is likely that PN will be required for a limited period of time – e.g. a patient with a temporary stoma formed high in the small intestine
- Those for whom the underlying disease causing the intestine to fail has an uncertain prognosis, but with the provision of PN can live an acceptable quality of life
- Those in whom the prognosis of the underlying disease is usually good and PN may need to continue for many years. PN may be reduced if intestinal adaption occurs and absorptive capacity improves. (DoH specialised service definitions http://www.dh.gov.uk/en/Managingyourorganisation/Commissioning/Commissioningspecialisedservices/Specialisedservicesdefinition/DH_4001679)

There was an upward age shift overall from 1996 and 2001, the commonest age range for new patients on HPN was 41- 60 years accounting for 50% of new registrations.

The majority of patients lived relatively independently on HPN, however there was a change in practice across the UK shown by the rate of independent living new registrations falling from 75% in 1996 to 55% 2001(BAPEN position paper 2003).

The prevalence of HPN is much higher in the USA than in Europe as much as 3-10 times greater (244). This is perhaps explained by the lack of a unified health care system in the USA where hospitals benefit from rapid patient discharge and both insurance companies and hospitals want all nutrition dependant patients home as soon as possible (245).

1.7.2 Paediatric Prevalence of HPN

Epidemiological data based on nationwide series of children do not exist (4). The 2007 BANS report 10 new paediatric HPN registrations which was the lowest number recorded since 2001. This is perhaps due to the fall in the number of reporting centres, (in 2005 there were 10 reporting centres which fell to 3 in 2006). Point prevalence - 95 and period prevalence -107, was not considerably different from 2006. The age distribution of new and established registrations have changed with the 6-9 years being the most prevalent. It is interesting to note that the 13-15 year olds have increased over the period 2000-2006 which represents the children on permanent HPN getting older (246).

There seems to be little recent data on prevalence of paediatric HPN in the USA. In 1988 it was estimated that children accounted for 14% of new registrations. Extrapolating from the 1988 data Colomb and Ricour suggest that in 2003 at least 16,000 children could be involved in HPN programs (247). However it is estimated that HPN in the USA is at least 10 times higher than in Europe (248).

1.8 Indications for HPN

Adult and paediatric PN is not so much a treatment for a disease as it is a treatment for a complication, notably intestinal failure common to a wide spectrum of diseases (249). It is important when looking at HPN therapy to consider the primary diagnosis, as the disease more than the therapy dictates the clinical outcome (176).

1.8.1 Indications for Adult HPN

In the UK the commonest indications for adult HPN are Crohn's disease, mesenteric vascular disease, volvulus and surgical complications, which can all lead to short bowel syndrome. Other disorders include intestinal fistulae, sequelae of radiation damage (radiation enteritis) and motility disorders including pseudo-obstruction syndromes and systemic sclerosis. Malignancy accounts for less than 5% of HPN in the UK which is in contrast with the some countries in Europe and the USA where cancer is the most common indication for HPN.

In 1995 Howard et al (176) published a nationwide survey of Home Parenteral and Enteral nutrition in the USA from 1989-1992. They estimate 40,000 patients were receiving HPN, cancer being the most common diagnosis. This is perhaps reflected in the average treatment time of 60 days. Younger patients had better survival rates, a greater likelihood of resuming full oral nutrition after 1 year, but they also had more frequent readmission for HPN related sepsis compared with older subjects.

A widening of the age spectrum of patients who started receiving HPN is seen, but the authors do not suggest an explanation for this finding. Younger patients generally had a better outcome, but the quality of the clinical outcome was good in all groups which made it reasonable to conclude that age per se should not disqualify anyone from HPN therapy.

1.8.2 Indications for Paediatric HPN

There is a general consensus in the literature that about 80 % of indications necessitating HPN in children are primary digestive (GI) diseases (247) including short bowel syndrome (SBS), Inflammatory Bowel Disease (IBD), Chronic Intestinal Pseudo-obstruction (CIIP) and Intractable Diarrhoea (ID). Some of the primary non digestive diseases include immune deficiency, malignancy, cystic fibrosis and radiation enteritis. Indications for paediatric HPN have been reported to be the requirement for a return

home for a period of greater than 3 months and the wish to preserve the QoL for the child and the family (200).

Table 1.3: Indications for HPN in Children

Disease	UK - 2006 (246)	France – 2007 (249)	USA - 1987 (31)
Primary GI Disease	86.5%	76%	79.5%
SBS	<5%	47%	33.3%
IBD	<5%	11%	21.5%
ID	15.8%	26%	14.7%
CIP	26.3%	10%	9.8%
Gastroschisis	9.4%	Within SBS data	Within SBS data
Autoimmune Enteropathy	8.4%	Within ID data	Within ID
Malignancy	<5%	2.3%	9.8%
Immune Deficiency	None reported	13.5%	None reported
Miscellaneous	None reported	10.2%	10.7%

Table 1.3 shows the latest published figures from the UK, France and the USA. The most recent reports from the USA do not distinguish clearly between adult and paediatric cases (176;250;251). The latest data from which conclusions can be drawn regarding the paediatric population was from 1987 (31).

A review of the literature highlighted the difficulty in comparing different series. There are discrepancies in classification of indications. When broader criteria are used and specific subgroups are not indicated, for example SBS or ID, it is often possible that a disorder can be included in either criterion, for example Crohn's disease can be included in both the SBS and IBD categories.

Interestingly the UK experience appears to differ greatly from France and the USA, <5% being those with SBS and IBD. The authors of the report do not comment on this.

1.8.3 HPN in Cancer/Immune Deficiency

HPN is a therapy considered for conditions where weight loss results primarily from increased catabolism, due to infections such as HIV or secondary malignant disease (11). In different clinical situations, a patient with cancer may benefit from HPN, for example, where a patient has a potentially curable cancer in which treatment may cause temporary bowel dysfunction, or where curative treatment has required massive bowel resection or abdominal radiation (252). Ethical problems start to arise when considering the terminal nature of untreatable malignancy.

The primary purpose of cancer treatment is to improve the quality of patients' lives by either curing their disease and/or ameliorating their worst symptoms for as long a period as possible (253). If a patient is expected to die earlier because of tumoral spread rather than starvation, there is no role for nutritional support (254;255).

The use of HPN in malignancy and immune deficiency syndromes is often controversial; however it is not a new phenomenon. Copeland et al was the first group to initiate a TPN program for malnourished cancer patients, allowing those patients to withstand the inherent complications of intensive oncologic therapy (116). As early as 1970 authors report the use of TPN in 26 cancer patients (117) and from 1978 reports of the use of HPN for cancer in both adult and paediatric series started to emerge (31;156;176;177;182;225;250;256). The use of PN in active cancer was initially debated, due to questions regarding the potential for acceleration of tumour growth and possible septic complications (257), however further study demonstrated that PN was safe and efficacious in oncologic patients (258;259).

HPN therapy in immune deficiency started to appear in the early 1990s, however the incidence of infection in relation to HPN treatment has been found to be high compared to other groups. This was explained by the special susceptibility of AIDS patients to infections and the frequent use of the nutritional catheter for antibiotic therapy or other purposes (260) and HPN use seems to have decreased due to more efficacious therapies (261).

It is now well reported that the practice of providing HPN in malignancy differ throughout the world (11) and there are wide differences in culture on what is considered appropriate use for HPN. In the UK it is comparatively uncommon and it is seen more in North America (262) and other countries in Europe such as Italy (170). Violante (263) report that out of 140 patients studied, 88% of the HPN recipients had cancer.

Jonkers-Schuitema (264) wrote an excellent editorial on the controversial use of HPN in palliative care, and presents both positive and negative points of pursuing this path. The terminal nature of malignant disease and AIDS means that patients usually only survive for short periods, and patient selection is very important (170). HPN is life prolonging, but only of value if the quality of life for both the patient and carers is also preserved. The current literature states that the majority of patients with incurable metastatic disease should not receive TPN at home (257;265-268). However Hoda et al (269) found that TPN can increase long term survival in very select patients with incurable cancer. Bozzetti et al (270) was the first to publish QoL data in a series of 69 advanced cancer patients receiving HPN, their main reason for nutritional support was the attempt to prevent an early death due to starvation in aphagic or obstructed patients. They concluded that it may benefit patients who survive longer than 3 months, yet in a further report go on to state that there is scarce accuracy of prediction on the length of survival in malignancy (271). In 2004 Orevall et al (272) found that the desperate and chaotic nutritional situation in the family led to a willingness to accept HPN and that it was viewed as a positive alternative. This study was followed up by further paper in 2005 (273) which discussed the views and experiences of HPN in the same population. They conclude that physical, social and psychological benefits were gained from HPN.

One of the main concerns of the use of HPN in malignancy is its fluctuating identification as a treatment or just basic care. Obviously some countries consider it a palliative type of medical intervention (263), while others believe wasting in malignancy appears to relate to a range of tumour induced metabolic disturbances, involving cytokines and appetite inhibiting peptides. Under these circumstances, nutritional support may not effectively redress the wasting but does expose the patient to the risks associated with parenteral

nutrition (274). Experience reported in the literature states that the preservation of nutritional status from progressive deterioration is a more common outcome than its restoration to normal (270).

1.9 Complications of HPN

HPN is a complex procedure and complications, although not always fatal, can result in increased hospital readmissions and increased costs, thus resulting in a series of poor outcomes (275). This was recognised as early as 1969 in infants (127;276). The most common complications of HPN are catheter related sepsis, catheter occlusion, liver disease and metabolic bone disease.

1.9.1 Catheter Related Sepsis

Both adult and paediatric HPN patients can have fever from many causes, but if no symptoms or signs point to other causes, the chief concern becomes catheter related sepsis.

Adult Catheter Related Sepsis

Although septic events are rarely fatal, they are the most common type of catheter related problem (>80%) and the most frequent reason for hospital readmission, so prevention is an important issue (277). Prevention of a septic episode may be much less expensive than treating one (116). Catheter infections are generally secondary to touch contamination and patient education. Less commonly infection can result from the infusion of contaminated fluids (252). Nursing technical expertise and compliance monitoring are vital components for preventing infections (275). Aggressive antibiotic treatments are often initiated to salvage a patient's catheter and prevent removal or replacement (278). Catheter sepsis rates have been shown to be decreased in very long-term HPN survivors (279) and in patients whose underlying disease was stable (12).

In adults, the latest published data reports a range of 0.31-0.35 episodes of sepsis per patient year (76;170;280;281). Coagulase-negative staphylococcus is the most common

CVC infection in adult HPN patients followed by Klebsiella pneumoniae, Staphylococcus aureus, and Enterococcus (282;283).

Paediatric Catheter Related Sepsis

In paediatric HPN, catheter related sepsis no longer represents a major cause of death (4). It is difficult to assess whether sepsis is a result of poor training or execution, or is a consequence of a more complex underlying disease which facilitated the occurrence of infection (4) Catheter removal is necessary in case of fungal infection, exit site cellulitis or tunnel infection, secondary infection or unsuccessful antibiotic treatment (182).

Sepsis occurs more in children than adults (224). Risk of CVC related infections in children has been found to be higher in children requiring HPN from early infancy than those started after the first year of life (196), higher in the first 2 years of HPN (224;284;285) and with SBS and neuromuscular intestinal disorders (286), and lower in patients with CIPS (284) and intractable diarrhoea (287). Patients with SBS and neuromuscular disorders display a high frequency of intraluminal bacterial overgrowth due to dysmotility which may be responsible for the increased prevalence of sepsis (286). Staphylococcus aureus and coagulase negative staphylococcus are generally the most frequent bacteria found in positive cultures (285). The incidence of CVC related infection has been reported to be between 0.41 - 0.78 episodes per patient year (224;284).

1.9.2 Catheter Occlusion

Catheter occlusion is a common complication of central venous access devices (275) where the lumen of the catheter becomes blocked or occluded. It may be caused by faulty catheter care, inappropriate infusion regimen (170) or secondary to drug thrombosis (288) It has been reported to occur at a rate of 0.071 episodes per patient year in adults and paediatric HPN (170) and is twice as common in those with congenital bowel disorders (289).

1.9.3 Venous Thrombosis

Venous thrombosis is a result of fibrin deposition and venous clot formation (290) and may be associated with catheter sepsis (277). Richards et al systematic review of HPN found the overall rate in adult and paediatric HPN to be 0.027 episodes per catheter year (170).

When a catheter is removed, local scar tissue develops resulting in the loss of an access site. Loss of venous access can ultimately result in higher rates of mortality in HPN (37), so preservation of venous access is of paramount importance.

1.9.4 Liver Disease

Hepatic complications can present as a broad spectrum of pathologic entities, including steatosis, cholestasis, steatohepatitis, fibrosis and cirrhosis (291-296). These complications are reported to occur in adults and children at a rate ranging from 15-85% (292;293;297-300). The rate and extent of development of HPN related liver disease can be influenced by many factors including the presence of SBS (298;299), intestinal bacterial overgrowth and translocation. It is thought that one of the causes is when an excessive intake of glucose causes sugars to be transported to the liver and converted into fat that cannot then be transported to peripheral fat stores, resulting in massive steatosis of the liver (116). Mildly abnormal liver function tests are well documented in prolonged parenteral feeding, and in most patients these abnormalities remain stable. However in a few patients more serious hepatic dysfunction develops eventually progressing to cirrhosis if not treated (277).

In 1979 the first documented case of TPN associated liver disease was in a premature infant who developed cholestasis (301). Patients with surgically induced intestinal failure are more likely to encounter HPN related liver disease (227), and it is more common in neonates who have recurrent episodes of sepsis and is reported to develop in 40-60% of infants on long term PN (200;302). In adults liver disease has been reported to occur in between 8-14% of patients (76;281) and is more common in SBS patients (277).

1.9.5 Metabolic Bone Disease

Metabolic bone disease refers to the conditions that are characterised by a diffuse decrease in bone density and strength (303). It has been suggested that 40-60% of patients on HPN have histologic features of decreased bone density or metabolic bone disease (304), and that 40-100% of adults may have some degree of bone demineralisation (304-306). The incidence of metabolic bone disease in the adult and paediatric HPN population remains unknown (303;307). In 2002 Pironi et al conducted an international multi-centred study on the prevalence of HPN bone disease and found that bone disease was present in most of the adults on HPN (84%) and that it was severe in half and symptomatic in one third of the population studied (305). The pathogenesis of HPN related bone disease is poorly understood, and is probably multi-factorial (308). Further research is needed to better understand its pathophysiology and treatment. It is a debilitating complication which may render the patient immobile and cause substantial pain (37).

1.9.6 Other Complications

Other complications include both medical and psychosocial maladies (34). Renal dysfunction (309) and neuropathological problems (310) have also been described in patients on HPN. Metabolic complications are more frequent in patients who can not have any oral intake, in those receiving glucose and lipid infusion greater than 6mg/kg/min and 3g/kg/day respectively and after long term administration of unbalanced formula (311-313).

Children fed with prolonged HPN may experience difficulty in establishing oral feeding, but little attention has been focused on the major behavioural difficulties these infants can experience (314). Developmentally non-oral feedings, especially during infancy, may interfere with the association of eating as a pleasurable experience (315).

HPN complications can be reduced with good training, meticulous aseptic technique, careful monitoring and prompt response to clinical indicators. There are several case reports which demonstrate the provision of HPN for over 25 years (316-318).

1.10 Survival / Outcome in HPN

The introduction of parenteral nutrition has significantly improved the prognosis of patients with major abnormalities in which the use of the GI tract has been precluded for extended periods of time. HPN patient outcome is the result of several factors such as evolution of the underlying disease, general clinical condition, level of care and family and social support (263). The overall prognosis of HPN patients depends on the prognosis of the underlying disease (61).

1.10.1 Adult Data

All human beings will eventually die, and to properly assess or interpret mortality rates in a population you either need a critical comparison of a similar cohort, or you need to evaluate observed versus expected mortality. Unfortunately data of this nature was not available. A simple review of the literature demonstrated that HPN patients in the UK had varying observed total death rates (see table 1.4) over the various time periods studied. This table does not indicate total mortality, but highlights the fact that the majority of deaths in this cohort were unrelated to the HPN and could be attributed to the underlying diagnosis or another medical illness. It is however difficult to clearly define if a death is clearly due to HPN or not. For example if a patient on HPN commits suicide, could this be attributed to HPN therapy? In the Freshwater series, the one death related to HPN was due to septic central vein thrombosis (281). In the Lloyd series, 3 deaths were due to septicaemia resulting from CVC infection and two deaths were due to hepatic failure resulting from HPN related liver disease (76). The one HPN related death in the Green series was due to line sepsis (280) and the O'Hanrahan paper uses the term HPN related deaths, but does not elaborate on specific causes (225).

Table 1.4: Adult Death Rates in UK HPN Patients

Paper	Year	N	Study Period	Total Observed Deaths (%) over the study period	Deaths Stated to be clearly due to HPN (%)
(76)	2006	188	1979-2003	55 (29)	5 (9)
(280)	2008	88	1990-2004	12 (13.6)	1 (1.1)
(281)	2005	23	1989-2002	9 (39.1)	1 (4.3)
(225)	1992	400	1977-1991	69 (17)	15 (22)

The latest data from the UK shows that overall probability of survival is 86%, 77%, 73% and 71% at 1, 3, 5 and 10 years. An almost 3 fold risk of death in patients starting HPN at >55 years compared to those starting at <54 was observed. Patients with SBS have the most favourable outcome, while GI dysfunction/dysmotility (pseudo-obstruction, radiation enteritis or systemic sclerosis) are associated with a threefold increase in mortality, and intestinal obstruction is associated with a six fold increase in mortality. Unsurprisingly survival is poor in those with an underlying diagnosis of neoplasia. No association between small bowel length and prognosis was found. Continued dependence on HPN was seen in 89%, 87% and 84% at 1, 3 and 5 years (76).

1.10.2 Paediatric Data

Although there are a number of articles which look at the outcome/prognosis of HPN, they lack specific details about the nutritional support received and do not clearly distinguish between adult and paediatric data (176;225;250;251), and have been excluded from the table 1.5 below.

The recovery of enteral autonomy, if it occurs, is almost always within the first 2 years in adults, but in children recovery can take much longer (251).

Table 1.5: Outcome of Paediatric HPN

Author	Year	Country	N	Still on HPN* (%)	Weaned (%)	Death (%)	Death due to HPN (%)
Vargas (31)	1987	USA	102	21 (21)	51 (50)	31 (30)	13 (41)
Ricour (200)	1990	France	112	45 (40)	49 (44)	18 (16)	2 (11)
Weber (83)	1991	USA	9	1 (11)	7 (77)	1 (1)	0 (0)
Candusso (218)	1995	Italy	19	5 (26)	10 (52)	3 (16)	0 (0)
Candusso (287)	2001	Italy	36	15 (42)	14 (39)	7 (20)	4 (57)
Holden (202)	2001	UK	38	32 (84)	2 (5)	4 (10)	1 (2)
Colomb (249)	2007	France	302	78 (26)	163 (54)	48 (16)	11 (24)
BANs (246)	2007	UK	79	51 (65)	16 (20)	12 (15)	0 (0)
Total	-	-	697	248 (35)	312 (44)	124 (17)	31 (4)

* Patients who were still receiving HPN at time of publication

There are 2 errors in the Vargas et al paper (31), the numbers of patients still on HPN, weaned and deceased add up to 103, yet the authors are reporting 102 patients. Also they state the number of patients on HPN for malignancy was 11, but this does not correspond with the table which only accounts for 10.

It is of interest to note that the in Colomb series 13 patients underwent small bowel transplantation, of which 11 survived, although 5 patients had to restart HPN after transplantation failure (249).

1.10.3 Significance of the Underlying Disease in Paediatric HPN

To try and determine the significance of the underlying disease data regarding the cause of death was analysed from each of the papers from table 1.5.

Table 1.6: A Breakdown of all Causes of Paediatric HPN Mortality from Table 1.5

Complication	**N (%)**
Underlying disease	79 (63.7)
Catheter related sepsis	15 (12)
TPN induced liver failure	12 (9.6)
Unknown	9 (7.2)
Other/Miscellaneous	6 (4.8)
Haematological complication of lipid emulsion administration	1 (0.8)
Nursing error	1 (0.8)
Fluid overload	1 (0.8)
Total	124

The data in table 1.6 clearly shows that the biggest influence on survival is the underlying disease, the significance being sufficiently strong that broad international agreement has been reached to describe outcome in terms of the specific primary disease (176;261;319;320).

The prognosis is poorer for patients treated for malignancy, immune deficiency disease (31) and intractable diarrhoea (249) and better for congenital short bowel syndrome (200;321) and IBD (249). Age also has an impact on survival, the younger the child at the start of HPN, the higher the risk of death (249).

1.11 Cost Issues

Clearly HPN is preferable to inpatient TPN both in terms of patient satisfaction and cost (225). There are studies from the UK (199;322), USA (323-327), Canada (328) and France (329), which examined the economic aspects of HPN and showed that HPN was between 65%-85% cheaper than alternative hospital treatment, making it considerably more cost effective and freeing beds in tertiary care facilities (210). However the data in these studies do not use the same methods to estimate costs, making it difficult to

compare when also taking into account different currencies, time scales and inflation. There will be difficulty interpreting the data until there is a consensus regarding expression of the result.

The majority of economic appraisals of HPN use cost utility analysis, the 2 most cited cost utility studies are from Canada in1986 (328) and the UK in 1996 (322). Detsky et al showed HPN gave an estimated net saving of Can $19,232 per patient over 12 years (328). The data from Richards et al suggested that HPN was more cost effective than hospital care, that the cost utility of treating younger patients was more favourable than treating older patients and that the estimated cost of HPN for an adult with benign disease in the UK was £36,000 per year after an initial £45,000 cost, with a calculated cost of £69,000 per quality of life year (322). To date there are no published extensive economic appraisals of paediatric HPN and several paediatric reviews are based on adult data (330;331). One study estimated that even in stable children on HPN the average cost was £159,000 over 30 months (332).

Some of the typical costs of an HPN programme include clinic visits, drugs, laboratory tests, nursing visits, inpatient episodes, pumps, intravenous solutions (327) training of patients, consumable and disposable supplies (331).

In France, Canada and the UK the financial burden of HPN is borne almost entirely by the NHS. In the USA third party carriers pay 80% of the costs with many patients finding it hard to pay the balance (331). In the USA to qualify for Medicare reimbursement HPN must be required for at least 3 months, fat malabsorption must be documented and enteral feeding must have failed (10). In the UK, often the obstacle in discharging patients home is organisation of the finance (199). However this may not be the case for much longer due to recent budget changes in the NHS, meaning that the hospitals will now only pay for the first 14 days of TPN and thereafter the primary care trusts are billed for the service. Paediatric studies have found that financial savings to the acute hospital trusts can be made if the rate of CVC insertion is reduced (333). Costs are also reduced because of the change of the labour force from professionals to carers or parents (228).

1.12 Small Bowel Transplantation (SBTx)

1.12.1 Adult Small Bowel Transplantation (SBTx)

If successful, SBTx restores the ability of digestion and can result in weaning from HPN sometimes within as little as 4 weeks (334). Although Small Bowel Transplantation (SBTx) is seen as a relatively new discipline, intestines were actually one of the first organs transplanted in man (335), and the first attempts documented were in 1967 (336). However success with intestinal transplantation has lagged behind that of other solid-organ transplants partly due to the advanced state of malnutrition and chronic illness seen in most patients referred (337).

In the late 1990s the issue of SBTx started to emerge as it evolved from an experimental procedure to an invaluable treatment for patients with intestinal failure and life threatening complications of HPN (334). The early experience of SBTx was restricted by intense graft rejection. In 1989, a study of the use of immunosuppressant Tacrolimus (FK506) in intestinal transplant patients (3 adults and 6 children) (338) demonstrated improved outcomes. However, poor outcomes are still limiting the widespread application of this procedure and even in the most recent era, SBTx still does not match but approaches survival of adult patients dependant on TPN (320;339), and HPN is still considered the primary therapeutic option (44) for irreversible intestinal failure.

In the UK the Department of Health, through the National Commissioning Group (NCG), recognises and funds 4 units for small bowel transplantation, 2 adult centres; Addenbrookes Hospital, Cambridge and John Radcliffe Hospital, Oxford, and two paediatric centres: Birmingham Children's Hospital and King's College Hospitals.

1.12.2 Paediatric Small Bowel Transplantation (SBTx)

Paediatric SBTx is feasible even in small infants and good intestinal function and independence from HPN has been achieved in children (340).

It has been recommended that children with chronic intestinal failure be identified and referred for assessment for SBTx early, in optimal nutritional status before liver dysfunction is established (341), as paediatric survival and recovery following combined liver and intestinal transplant is probably lower than following an isolated transplant. Also, recipients of an isolated intestinal allograft tend to wean from PN more quickly – median time 27 days, compared to 40 days for a combined liver and SBTx (342). A multidisciplinary approach to SBTx is thus vital, Beath et al (341) noted marked discrepancy between children referred for evaluation from centres with and without nutritional care teams, children coming from hospitals with multidisciplinary care teams were better nourished and had fewer CVC infections.

One issue that may impede paediatric SB transplantation is donor recipient size incompatibility. Most candidates have had massive bowel resections with a subsequent reduction in the size of the peritoneal cavity. Therefore they often require donors who are 50-75% smaller, thereby limiting the field of potential donors (43).

Both HPN and SBTx can be highly effective treatments of intestinal failure, but each have a specific psychosocial impact and are capable of permitting children a normal participation in society (221). For approximately 6-12 months post transplantation, care routines of transplanted patients may include up to 15 daily medications, tube feedings, intravenous fluids and maintenance of the gastrostomy tube, jejunostomy tube, ostomy and central venous catheter. These routines decrease over time, but a mean of 7 daily is still required at >3 years (343). In a recent study the majority of parents state that caring for their post transplant child is easier than before transplant (221), although hostility and obsessive compulsive dimensions related to post operative adjustment have been reported in parents or carers in the postoperative period (344). It is interesting to note that in one study only six families (out of 14) said they would consider (paediatric) bowel transplantation (202) possibly suggesting that the majority were satisfied with HPN.

1.12.3 Indications for SBTx

In September 1991 an Intestinal Transplantation (IT) program was initiated in Los Angeles USA (345). They were the first group to suggest criteria for SBTx and transplantation criteria continues' to be debated. However the most recent adult and paediatric transplant criteria as defined by Medicare in the USA are (10): "failure of HPN therapy" by the development of one or more of the following complications:

- Impending or overt liver failure
- Thrombosis of major central venous channels (2 thromboses in subclavian, jugular or femoral veins)
- Frequent CVC sepsis (2 episodes of systemic sepsis secondary to CVC infection per year, 1 episode of CVC related fungemia, septic shock or acute respiratory syndrome)
- Frequent severe dehydration

This is in contrast to the American Society of Transplantation paediatric guidelines which include patients at high risk of death from their primary disease or with high morbidity intestinal failure and which emphasise the need for preserving vascular access (342).

The rate and the indications for adult and paediatric candidacy for transplantation differ, the rate being nearly twice as high in paediatrics and the indications being mainly related to the high risk of death related to the underlying disease (pre-emptive transplant), whereas in adults its mainly due to the failure of HPN (346).

1.12.4 Adult and Paediatric SBTx Current Figures

The Intestinal Transplant Registry is a collaborative effort among all centres performing intestinal transplantation which reviews the worldwide experience of SBTx (http://www.intestinaltransplant.org/). The Registry data is collected every two years from each centre and a report is produced. As of May 2009, there are 73 centres worldwide which have performed 2188 intestinal transplants in 2038 patients. The main condition leading to both adult and paediatric transplantation was short gut (58% and

68% respectively). Advances in surgical, clinical and immunosuppressive management since 1995 have improved patient survival and currently one year survival is approximately 80% and 5 year survival is approximately 50%. Waiting at home and being transplanted at a high volume centre are associated with superior survival rates, while the presence of a concurrent liver graft is associated with better long term survival (M. Marquez MD, Intestinal Transplant Registry Data November 2009, personal communication 3rd November 2010).

1.12.5 QoL After Intestinal Transplantation

If a patient on HPN has a satisfactory QoL, at which point should they be referred for SBTx assessment? QoL issues surrounding HPN and SBTx have been studied, but as yet no adult or paediatric study has clearly demonstrated a difference in the QoL between stable patients on HPN and transplant patients (277;342).

Small bowel transplantation in adult and paediatric recipients offers a realistic alternative to HPN and often the choice of treatment is highly influenced by expected QoL outcomes.

When intestinal failure is irreversible, and dependency on HPN becomes life long, SBTx can be a considered as an alternative treatment. Obviously if HPN treatment fails, then SBTx must be considered. This is a black and white picture as there is really no alternative and so often is considered as a last resort. Unfortunately this means that patients referred for transplantation are often very sick resulting perhaps in poorer outcomes.

The issue of SBTx in patients who are well and managing on HPN is a greyer area. Whilst it would seem prudent to refer early, the poor outcome rates often halt this process. This is where the identification of QoL becomes essential. If a family and/or patient appears to be coping well with the HPN therapy, and QoL is deemed good, then is there a need for SBTx? Some authors suggest that most patients receiving HPN therapy do not develop life threatening complications and therefore have a prognosis superior to

that offered by SBTx (345). In practice, the Royal London Hospital tends to avoid referring patients for SBTx unless really necessary, as definitely, clinically HPN is considered a safer option.

Fiscal evaluations of SBTx yield no clear economic conclusions. HPN is as good as transplant, but the balance between it and prolonged HPN in terms of clinical and cost effectiveness and QoL remains equivocal (11). It is mandatory to assess carefully the respective costs of long term HPN and intestinal transplantation with the highest consideration for the best option in terms of QoL for both patients and their carers (347).

1.13 Definition and Origins of Quality of Life (QoL) Research

The biggest problem faced by those wishing to measure and quantify QoL lies in the definition of the term. Many definitions are ambiguous and therefore do not allow consistent and obvious methods of measurement. The origin of QoL measurement is a relatively new concept, and it is an area which is still evolving.

Politicians, philosophers, priests, psychologists, physicians and patients might all offer different definitions as to what constitutes QoL, and few of these descriptions would allow obvious and consistent methods of measurement (253).There is no consensus or absolute definition as QoL is conceptually a subjective term (253). But in 1993 the WHO defined QoL in relation to health as:

The perception by individuals of their position in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (348).

Previous generations understood very well that striving to keep people alive could be inappropriate. Historically medical workers have basked in the clear moral light of working to keep people alive (349). However it is in more recent times that issues surrounding the quality rather than quantity of life have arisen.

The concept and measurement of QoL entered medical research from two different sources – medical health status indices and social science population indices.

The developments of functional status indexes were designed to examine non-biologic and objective aspects of patient daily behaviour. Functional health status was defined as the ability to perform routine self-care, to complete basic activities and on the basis of the level of independent living. The first functional classification scale for adults was published in 1937 (350).

In 1948 the WHO defined health as: not only the absence of infirmity and disease, but also a state of complete physical, mental and social well being. This prompted governments to develop indexes designed to examine the social aspects of health, the personal impact and the steps taken to prevent illness, and the relation of medical care to other demographic variables.

The first mention of quality of survival in a clinical trial was not seen until 1966 (351), and the term quality of life first entered medical literature in this year, although the literature contained no specific instruments for measuring QoL until 1970 (352;353). In 1974, Social Indicators Research, a new journal which was dedicated to research on the QoL, was first published. The first QoL measure to gain popularity was Preistmans and Baums 1976 Linear Analogue Self Assessment Scale (354).

For the next decade QoL instruments were appraised and developed. However in the mid 1980s two events provided the impetus for measuring QoL in clinical trials. Firstly in 1985 the Food and Drug Administration decided that QoL data was required as one of the key efficiency parameters in clinical trials. This resulted in the need for validated QoL instruments. The second event occurred when QoL data was for the first time a primary outcome in a clinical trial (355) to assess the QoL of patients taking one of 3 hypertensive medications. Soon it became obvious to pharmaceutical companies that their products could be promoted, not just for physiologic effects, but also for effects on QoL.

1.13.1 Types of QoL Measurement

There are now a plethora of QoL instruments available to health professionals, which can be generic, disease specific or global.

Generic instruments are used in general populations to assess a wide range of domains applicable to a variety of health states, conditions, and diseases.

Disease specific questionnaires are designed to be used in populations with specific diseases. The questions are well defined and aim to detect aspects of the disease which are thought to have an impact on QoL. Disease specific questionnaires are also useful in determining the impact of interventions designed to influence symptoms of the disease.

Global measures are those designed to measure QoL in the most comprehensive or general manner. This may be a single question that asks the respondent to rate their QoL, or an instrument such as the Flanagan QoL scale (356) that asks respondents to rate their satisfaction on 15 domains of life.

The number of items in the questionnaire relates to the actual number of questions to be answered. The advantage of questionnaires with a small number of items is that people rarely mind completing them, however it is often harder to draw meaningful analysis unless you have a large sample size, and conclusions are very general due to the limited nature of questions. A questionnaire with a large number of items can be used to obtain more information, yet completion can often be poor meaning missing data has to be negotiated.

Administration of the questionnaire is an important factor to consider in choosing the instrument. Questionnaires are designed to be completed by self administration, by an interviewer, or by telephone, and in rare cases to be used in group sessions. Weinberger et al (357) reported telephone and interviewer administration produced fewer missing data than self administration. It would be inappropriate to expect a respondent to complete a questionnaire on their own when it is designed to be administered by an

interviewer. Many of the questionnaires have been adapted for administration over the telephone. In these cases a strict script has been developed which must be adhered to. It is vital that the telephonist does not influence the respondents answers, as it may lead to over optimistic data (358).

For some instruments there is a normative database available. A known database can be an essential method of comparison between different populations. Community norms are important as they provide a base level of results on the questionnaire (359).

Time recall is the point in time upon which you are asking patients to rate their QoL. Many of the questionnaires try to illicit how a person currently feels, whereas others are more concerned with how a person has been feeling over a set period of time – for example over the last month. When choosing which instrument to use you must decide what time recall is appropriate for your population.

A suitable QoL instrument should have been subjected to extensive studies of psychometric properties such as reliability, the tendency to answer questions in a consistent manner, and validity, the tendency for respondents' answers to correspond with their other known characteristics. QoL evaluation is part of the skilful clinician's armamentarium (360).

1.13.2 QoL Measurement in Paediatrics

Health Related QoL (HRQoL), health status and functional status are terms often used interchangeably to describe patients' perceptions of their health, but HRQoL is considered the more comprehensive term (361;362). Much of the impetus for more formal measurement of child QoL has come from work in paediatric oncology and neonatal intensive care (363). The first formal attempt to measure paediatric QoL in 1985 is often credited to Lansky et al whose measure remains in use today (364).

In paediatrics several issues, including cognitive development considerations complicate the decision regarding the best respondent for HRQoL assessment. Some measures allow for self report while others rely on a proxy such as a parent, teacher or clinician to rate the child's HRQoL. However, self report and proxy report often do not agree. Research has demonstrated that children younger than 5 are not able to self report their health and well being (362). Parents have been shown to be better able to rate externalising (physical) compared to internalising (emotional or social) problems (365) and they may also be influenced by the development of other children they know, their expectations and hopes for their child, additional life stresses, their own mental health (366) and the burden of care giving (367). It has been shown that agreement is better between parents and chronically sick children compared with parents and healthy children (367).
All currently available paediatric measures have some limitations (363), are few in number and still in the early stages of development (362). Among disease specific measures, asthma, cancer and epilepsy have received most attention. For children with other conditions it is only possible to rate QoL using generic measures (366).

1.13.3 Quality of Life Instruments Database

The success of QoL research greatly depends on the choice of appropriate instrument. In 2002 the Quality Of Life Instruments Database (QOLID) project was initiated to provide a comprehensive and unique source of information on QoL measures, which is available through the internet (http://www.qolid.org/proqolid/). Its aims are to provide an overview of existing instruments, to assist in the choice of appropriate instrument and to facilitate access to instruments and their developers (368).

A search engine allows criteria based queries to be made including type of instrument, pathology, target population, language and mode of administration. In 2008 the Quality of Life Instrument Database contained 72 adult generic instruments, 13 generic paediatric instruments and 33 instruments for digestive system diseases only one of which was designed for use in paediatrics.

1.13.4 Short Form 36 Questionnaire (SF36)

The 36-item short-form questionnaire (SF36), see Appendix 1, was constructed to survey health status in the Medical Outcomes Study (369). The SF36 was designed for use in clinical practice and research, health policy evaluations, and general population surveys. It has excellent reliability, validity and responsiveness (370). The SF36 includes one multi-item scale (36 items) that assesses eight health concepts:

- **Physical Functioning (PF)** - limitations in all physical activities including bathing and dressing due to health problems.
- **Role Physical (RP)** - limitations in usual role activities because of physical health problems.
- **Bodily Pain (BP)** – limitations due to pain.
- **General Health (GH)** – evaluates personal health.
- **Vitality (VT)** - evaluates energy and fatigue.
- **Social Functioning (SF)** - limitations in social activities because of physical or emotional problems.
- **Role Emotional (RE)** - limitations in work or other daily activities because of emotional problems.
- **Mental Health (MH)** – evaluates feelings of nervousness and depression.

Scores range from 0 – 100, the higher the score, the higher the QoL in that domain.
The survey was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone.
Normative data (age and gender specific) for the UK population is produced by the Health Services Research Unit Oxford (371).

1.13.5 Hospital Anxiety and Depression Scale (HADS)

The HADS (see Appendix 2) is a brief (14 item), self report measure of anxiety and depression developed by Zigmond and Snaith (372). It was developed for use in general medical outpatients clinics, but is now widely used in clinical practice and research (373). The Authors recommend that for the anxiety and depression scales alike, raw scores of less than 7 indicate no case, scores between 8 – 10 identify mild cases, 11 – 15 moderate

case, and 16 or above severe cases. However in 2001 normative data was produced for the UK from a large non clinical sample (374) which suggested a single higher cut off of 10-11 should be used to categorise cases as only moderate or severe.

1.13.6 EuroQoL 5 Dimensions Instrument (EQ5D)

The EQ5D questionnaire (see Appendix 3) is a generic measure of health status (5 items) developed by the EuroQoL group (375), an international research network established in 1987 by researchers from Finland, the Netherlands, Sweden and the UK. Health is defined in terms of 5 dimensions: mobility, self care, usual activities, (work, study, housework, family or leisure), pain or discomfort, and anxiety or depression. Each domain is subdivided into 3 categories which indicate whether the respondent has no problem, a moderate problem or an extreme problem in each dimension. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. EQ5D has been specially designed to complement other quality of life measures such as the SF36, Nottingham Health Profile (NHP), Sickness Impact Profile (SIP) and some disease-specific measures. In 1998 normative EQ5D data was published using a large sample of 3395 UK individuals representative of the general population (376).

1.13.7 The Ways Of Coping Questionnaire (WOCQ)

Stress is experienced as a developing dynamic reciprocal transaction. This means that the individual's interpretation with a stressor is neither a reaction nor a response, but rather a transaction between his or her appraisal of the level of threat to his or her well being. In other words, the individual feels stressed only when he or she assesses the event taxing his or her psychological resources. Coping involves the use of cognitive and behavioural strategies to deal with the demands imposed by the stressful experience (241). Mediators of stress are those behaviours, perceptions and resources persons use or posses to influence the experience and management of stressful experiences (228;377).

How individuals cope with stress, not stress per se, influences their psychological well-being, social functioning and somatic health. The WOCQ was developed to provide researchers with a theoretically derived measure that could be used to explore the role of coping in the relationship between stress and adaptive outcomes (378). It is designed to be both interviewer and self administrated.

The WOCQ (see appendix 4) consists of 66 items which aim to identify the thoughts and actions an individual has used to cope with a specific stressful encounter by measuring coping processes. The respondent is asked to think about the most stressful situation they have experienced within the last week. “Stressful” is defined as being a situation which was perceived as being difficult or troubling either due to the requirement of a considerable effort to deal with the situation or distress. It can include work, medical or car problems, discussion or confrontation, separation from someone you care about or something else.

The 66 items represent thoughts and actions that can be used to deal with stressful situations. The respondent rates each item on a 4 point scale from “not used” to “used a great deal” (235). Adequate reliability and validity have been demonstrated for the use of the scale with parents of disabled children (379). The WOCQ is reported to have good internal consistency with Cronbach’s alphas for the subscales ranging between 0.61 and 0.79 and also has a good construct and concurrent validity (241).

Eight scales are derived from the responses:

- **Confrontive Coping (CC)** – Describes aggressive efforts to alter the situation and suggests some degree of hostility and risk taking.
- **Distancing (D)** – Describes cognitive efforts to detach oneself and to minimise the significance of the situation.
- **Self Controlling (SC)** – Describes efforts to regulate one’s feelings and actions.
- **Seeking Social Support (SSS)** – Describes efforts to seek informational support, tangible support and emotional support.

- **Accepting Responsibility (AR)** – Acknowledges one's own role in the problem with a concomitant theme of trying to put things right. Accepting responsibility as a form of coping is more frequent in depressed people (241).
- **Escape Avoidance (EA)** – Describes wishful thinking and behavioural efforts to escape or avoid the problem. Items on this scale contrast with those on the distancing scale, which suggest detachment. EA corresponds to increased depression, isolation and spousal relationship problems (380)
- **Planful Problem Solving (PPS)** – Describes deliberate problem focused efforts to alter the situation, coupled with an analytic approach to solving the problem.
- **Positive Reappraisal (PR)** - Describes efforts to create positive meaning by focusing on personal growth. It also has a religious dimension.

There are 2 ways of scoring the WOCQ, raw and relative. Raw scores describe coping effort for each of the 8 types of coping, relative scores describe the proportion of effort represented by each type of coping. Relative scores are calculated from raw scores and describe the contribution of each coping scale relative to all of the scales combined. The relative scoring method controls for the unequal numbers of items within scales and for individual differences in response rates.
Families who use a variety of coping strategies function more effectively than those who only use one strategy exclusively (212).

1.13.8 The General Health Questionnaire (GHQ)

The GHQ (see appendix 5) is a validated (381), internally consistent self administered screening questionnaire designed to detect those with diagnosable psychiatric disorder (382). It assesses the respondent's current state, asks if that differs from their usual state and is thus sensitive to short term psychiatric disorders. There are several versions of the GHQ (GHQ12, GHQ28, GHQ30 and GHQ60). The GHQ28 is the most used and popular version of the GHQ possibly because it provides a profile of scores whereas the other 3

only yield an overall total score. There are 4 subscales (each containing 7 items) and an overall total score:

- Somatic Symptoms (SS)
- Anxiety/Insomnia (AI)
- Social Dysfunction (SD)
- Severe Depression (SevD)
- Total Score

Likert scoring is the most generally used method of scoring the GHQ28 producing a wider smoother score distribution for use when the severity is to be assessed. A suggested threshold (using the Likert scoring method) of greater or equal to 24 (out of a possible score of 84) identifies cases of positive psychiatric condition (381). There are no thresholds for individual subscales.

1.13.9 Functional Status IIR Measure (FSIIR)

The FSIIR - short version (see appendix 6) is a measure of child health status that is intended for use with children spanning the entire childhood range from 0-16 years old. It has particular strengths for the measurement of health status of children with chronic physical conditions who are not disabled. It uses a common core of 14 items which have been validated and shown to be internally consistent. It is designed to measure dysfunction only related to illness (383). It should be administered by an interviewer as it is divided into 2 parts. Part one is a series of questions asked to the parent or carer about how the child functions, for example, do they eat well? Do they sleep well? There are 3 responses, never or rarely, some of the time and almost always. When part one is completed the interviewer returns to the questions which indicate a neutral or negative response and illicit if the poor functioning is due to illness. This is used to determine whether an illness related pattern of behaviour exists. Scores range from 0 – 100, the higher the score the better the perceived functional status of the child.
In a sample of 732 children with and without a chronic physical condition, internal consistency testing showed a reliability coefficient of α=0.80 for all ages (383).

The authors of the FSIIR view behaviour as the final common pathway of health and defined the healthy child as one who exhibits age-appropriate physical, psychologic, intellectual and social behaviours (383).

1.13.10 McMaster Family Assessment Device (FAD)

The FAD (appendix 7) is a 60 item, self report, multidimensional measure of family functioning which has proven reliability and validity (384). All family members above the age of 16 are asked to complete the questionnaire in order to obtain an overall perception of how the family operates. When scores for multiple family members are obtained, results are averaged. The 7 dimensions of the FAD are:

- **Problem Solving (PS)** – The family's ability to resolve problems (issues which threaten the integrity and functional capacity of the family) at a level which maintains effective family functioning.
- **Communication** – The exchange of information among family members, focussing on whether verbal messages are clear with respect to content and direct in the sense that the person spoken to is the person for whom the message is intended.
- **Roles** – Does the family have established patterns of behaviour for handling a set of family functions which include provision of resources, providing nurturance and support. Supporting personal development, maintaining the family systems and providing adult sexual gratification.
- **Affective Responsiveness** – assesses the extent to which individual family members are able to experience appropriate affect over a range of stimuli. Both welfare and emergency emotions are considered.
- **Affective Involvement** – is concerned with the extent to which family members are interested in and place value on each others activities and concerns. The healthiest families have intermediate levels of involvement
- **Behaviour Control** – assesses the way in which a family expresses and maintains standards for the behaviour of its members. Behaviour in situations of different sorts (dangerous, psychological and social) is assessed as well as different patterns of control.

- **General Functioning** – Assesses the overall health/pathology of the family.

Scores range from 1-4 with 1 reflecting healthy functioning and 4 reflecting unhealthy functioning. The FAD differentiates between healthy and unhealthy family functioning and the authors have derived threshold/cut off scores for each domain. If the family scores above the threshold, this indicates some degree of family dysfunction in that dimension (384).

1.14 Quality of Life (QoL) in Adult Home Parenteral Nutrition (HPN)

HPN is a life saving, potentially life long therapy that allows patients with intestinal failure to be discharged from hospital and to live at home. However it is a therapy which can potentially seriously impair an individual's mobility and social life. It can be expected that these patients will perceive QoL differently from those who have a terminal illness. The major therapeutic goal for most patients with a chronic illness is not a cure of the disease, but rather an improvement in function and life quality resulting from an alleviation of the symptoms of the illness (385).

Initially HPN was reported to have a positive effect on patients' well being which was attributed to the reduction of gastro intestinal symptoms, weight gain and an increase in strength and exercise tolerance (159).

Early responses to permanent TPN were examined by Price et al in 1979 (386) who showed anxiety, depression, fear, negative body image, and major adjustment problems centred on the loss of the basic function of eating in Canadian patients. The reasons for the initiation of TPN were varied and included CIP and SBS. Intravenous feeding forced patients to make multiple alterations to their life styles. The ability to cope with this intrusive procedure was related to the level of restitution of physical health, ego, strength, and the family and hospital support systems. Sexual function was decreased in most cases with only occasional patients noticing improvements.

In 1981 Ladefoged (387) conducted a psychosocial survey of Danish patients on HPN, and concluded that 9 out of 13 patients had a fair quality of life. However no validated QoL instruments were used. These interviews were repeated and revealed no systematic improvement or deterioration in QoL.

Detsky et al published Canadian data which suggested moving patients from hospital to home resulted in a significant gain in QoL (and financial savings) (388). In 1986 Mughal and Irving (243) described data from the UK HPN register (200 patients). QoL was crudely assessed by categorizing patients into one of 4 categories: 1) at work full time or looking after family and home unaided. 2) At work part time or looking after home and family with help. 3) Unable to work but able to cope with HPN unaided. 4) House bound needing major assistance with HPN. They found that the majority of patients were fit and independent whilst on HPN. Grade 4 was classified as an unsatisfactory QoL, and the patients who fell into this group tended to be older. The authors concluded that QoL is generally good in those whose intestinal failure is due to a disease affecting primarily the GI tract (e.g. Crohn's disease), but poor in those whose intestinal failure is a manifestation of a systemic disorder (e.g. scleroderma, malignancy and radiation enteritis). They also noted the tendency for QoL to deteriorate with time as the systemic disease advanced.

Stokes et al 1988 (389) described 76 cases – some of which were included in Mughal and Irving's UK data (243). They used the same 4-point system to assess QoL. They found that 35 of their patients fell into grades one and two, but did not discuss the patients who were in grades three or four. USA data from Burnes et al (390) (1992) found that age did not negatively impact on QoL, which is in contrast to O'Hanrahan and Irving's findings that older patients did less well (225). A further study in 1993 used the 4 point Mughal criteria for assessing QoL and found HPN improved QoL by ameliorating the protein calorie nutritional status, allowing social rehabilitation and reducing the hospitalisation rate. Two thirds of their patients could be considered fully or partially rehabilitated.

The Canadian 1979 Price and Levine paper (391) comprehensively studied the psychological and social responses to the early stage of HPN. They found that the patient goes through a series of stages beginning with numbness, disbelief or denial, thereafter a period of pain, sorrow, eventually ending up with acceptance and adaptation to a new way of living. Depression, anxiety and body image comprised the early emotional reactions. Adaptation involved coming to terms with lack of control over body functioning and dependence on mechanical apparatus to sustain life. Resumption of normal activities was essential and included employment, sleep, marital relationships, sexual functioning and family involvement.

The first study of QoL which used validated questionnaires was from the USA and published in 1993 by Smith (392). She described psychologic, social and fiscal aspects of HPN from both the patients and the caregiver's perspective. Results indicated QoL, self-esteem, life satisfaction, family cohesion and quality of the patient – caregiver relationship to be similar to population norms, and noted that family adaptability and coping scores were higher than population norms. Overall a low QoL score was associated with increasing length of time on HPN – for both patients and caregivers. Problems such as loss of friends, employment and depression were reported in two thirds of families.

A UK study in 1997 by Richards et al (393) reported the extent to which opiate and benzodiazepine dependence affected outcomes for patients on HPN. Health status was measured using the SF36 and EuroQoL instruments. The data was from a series of 15 patients; 5 dependent and 10 controls (not dependent), and although it is not possible to derive statistically significant results from such small numbers, it is possible to identify trends. Results indicated that the QoL experienced by dependent HPN patients was lower compared to controls.

Another UK study by Egger et al (394) showed 51% of their HPN population to be moderately malnourished. Under-nutrition causes weakness, impairs immune function and reduces the ability to work (395). Jamieson et al (395) (UK) showed weight gain

significantly improved QoL scores in every category of the Nottingham Health Profile (NHP) in a group of previously malnourished patients. A further study by Richards and Irving (396) assessed the QoL of 51 patients on HPN using the same QoL instruments as the previous study (SF36 and EQ5D). Compared to earlier studies which suggested a large proportion of HPN patients were mostly independent and able to work (243;389;392), Richards and Irving found that 80% of patients reported that they were too ill to work. The SF36 scores were significantly lower than population norms in 6 (out of 8) domains: Physical Functioning (PF), Physical Role (RP), General Health (GH), Social Functioning (SF), Vitality (VT) and Bodily Pain (BP), and were at the lower end of the normal range for Mental Health (MH) and Emotional Role (RE). There was no difference seen between patients who were too ill too work or employed (although the number of patients actually employed was very small which prevented meaningful analysis). They found younger patients (<45) scored higher in PF, SF and RE than compared to older patients. No gender differences were observed. The EQ5D scores concurred with the SF36 scores. An Italian study of 30 HPN patients in 2001 (79) found that only the PF and GH were significantly lower than that of the general population which is in contrast to previous studies.

HPN has also been found to result in a reduction in steroid intake in Crohn's disease, and obviate the abdominal pain associated with eating. Decreased GI secretory activity can also result in a decrease in pain secondary to partial small bowel obstruction. Decreased stoma output or diarrhoea may lead to a marked improvement in social activity and general QoL (397).

To date the majority of studies which have measured QoL in HPN patients have used generic QoL questionnaires including the SF36 (79;327;393;396;398-402), EQ5D (393;396;400) and SIP (403;404). The disease or treatment specific measures that have been used to measure QoL in HPN include the IBDQ (404), Quality of life instrument/inventory (405;406), Quality of life index (392;402) and the Rotterdam symptom checklist (270). However, although these measures are disease or treatment specific, none of them are designed to be used in, or specific to the HPN population. The

IBDQ was designed to measure the subjective health status of patients with inflammatory bowel disease. It examines symptoms related to the primary disease, social function, emotional state and systemic symptoms (361). The Quality of life instrument/inventory was designed for use in transplant patients and examines emotional state, social and physical functioning pain and discomfort, relationships and vocation. The quality of life index was designed to be used in healthy individuals and renal dialysis patients (407), but has also been used in liver transplant patients. It measures satisfaction with regard to health, socio-economic status, psychological/spiritual and family life. The Rotterdam symptom checklist was designed for use in cancer patients, and measures physical symptoms (pain, fatigue and gastrointestinal complaints) and psychological distress (408). Often these disease or treatment specific questionnaires fail to measure HPN symptoms such as sleep disturbance and the psychological effects of not eating and drinking are not normally addressed (409), and have highlighted the need for a HPN specific QoL questionnaire.

Janet Baxter and her colleagues from the Scottish Home Parenteral Nutrition Managed Clinical Network, Ninewells Hospital and Medical School, Dundee, UK, have subsequently developed the HPN-QOL, a method of objectively assessing the QoL of patients treated with HPN. The HPN-QOL has been rigorously prepared and demonstrates psychometric and clinical validity to assess the QOL of long-term HPN patients (410). It is an exciting development in the field of HPN and results from clinical studies are eagerly awaited.

1.14.1 QoL After Intestinal Transplantation

In the 1990s small bowel transplantation was introduced as a possible alternative to HPN for the treatment of irreversible gut failure, but a mortality of 40 – 50% after 3 years was ascribed to initial attempts (406;411). In 1998 DiMartini and Rovera et al published two studies which compared QoL in HPN patients with those who had received intestinal transplantation. In the first study (406) both intestinal transplantation and HPN patients were retrospectively asked to rate their QoL over time. In the second study (405) analysis was confined to current assessment of QoL. They concluded QoL in post transplant

patients was similar to that of HPN patients, although QoL in the transplanted group improved over time with decreasing anxiety as they adjusted in the post transplant period. A study by Van Gossum et al of 228 HPN patients showed that only 8% of their population claimed a willing for intestinal transplantation, while it was considered by the medical team in 10% of the patients (412). The decision whether to refer a patient for consideration of small bowel transplantation may be difficult if the QoL on HPN is satisfactory (221).

In 1996 DiMartini et looked at psychiatric evaluations of small intestine transplantation patients (335). Faced with the complicated postoperative course, transplant recipients develop a range of endogenous and organic psychiatric disorders. They reported, 30 adults and 33 children who had undergone intestinal transplantation. Early in their program it became evident that psychiatric evaluation, support and treatment would often be necessary in the post operative phase. Half of their adult patients required psychiatric intervention at some point in the transplant process. Five patients developed adjustment disorders with anxious and depressive features in response to their prolonged hospitalisations and medical/surgical complications. Two patients required psychiatric intervention for delirium at later points during their hospitalisations. Patients with Crohn's may have a higher incidence of depression. It is extremely difficult to define or anticipate the amount of pain an individual is or should be experiencing, especially in this highly sensitive area. As knowledge advances they state they will be better able to serve the psychological needs of intestinal transplant candidates and recipients.

1.14.2 A Systematic Review

In 1997 a systematic review of HPN was published (170). The objective was to locate, appraise and summarise evidence from scientific studies on HPN in order to answer specific research questions on the effectiveness of this technology. The authors conclude that QoL is reasonable for patients with benign disease. Fifty six studies met the inclusion criteria, 13 of which attempted to measure QoL. However only five studies measured QoL using validated instruments, although it is not clear which studies these are.

1.14.3 Comparison of Adult HPN Patients and Different Patient Groups

QoL was compared between Home Enteral Nutrition (HEN) and HPN by Reddy et al in 1998 (327). They found no significant difference between the SF36 scores of HPN and HEN patients, although both groups scored significantly lower scores than the general population in 5 (out of 8) of the domains. As with other studies MH and RE were seen to be closer to population norms, but this study showed that BP was not significantly different. SF36 scores were also compared with patients on renal dialysis (413) because the patients were believed to experience similar interference with daily living. End stage renal disease and HPN patients both have chronic long term conditions and dependence on IV access, which interrupts their daily routine. No statistical differences were found between the two groups in any of the 8 domains.

Richards and Irving (396) compared SF36 scores of HPN patients (with Crohn's Disease) with age matched type II diabetics and patients with congestive cardiac failure. They reported lower scores in the HPN patients than both comparison groups in all 8 domains, however the diagram in the paper does not the support text – according to the graph (Figure 4 p.221), those with congestive cardiac failure have the lower SF36 scores than HPN patients.

Smith (392) found Quality of Life Index (QoLI) mean scores of HPN patients to be similar to those reported in groups of chronically ill patients requiring haemodialysis, peritoneal dialysis, liver transplant and chemotherapy.

1999 Jeppesen et al (404) studied QoL using the generic Sickness Impact Profile (SIP) and disease specific Inflammatory Bowel Disease Questionnaire (IBDQ). HPN patients were compared with 36 patients who had either anatomical or functional short bowel not on HPN. The HPN patients scored worse overall in both the SIP and IBDQ. The exception being the HPN had fewer problems with bowel symptoms. In agreement with Carlsson et al (399) the presence of a stoma was not associated with lower QoL scores and the authors postulate the impairment in physical, emotional and social function in the

HPN group may be related to the complex technology required for the nutritional support, rather than the inconvenience and bowel symptoms that accompany intestinal failure. They also agreed that QoL in HPN compares well with that reported in chronic renal failure.

A further study by Cuerda (403) also used the SIP to measure QoL, however only six patients were measured, and showed QoL scores were slightly decreased compared with normative data.

The most recent study published on QoL and HPN was in 2003 (399). Its primary aim was to assess QoL in patients with short bowel syndrome – 8 of whom were on HPN. It agrees with other studies in that patients receiving HPN rated lower QoL scores than those with intestinal dysfunction not on HPN. Fear of becoming a burden was the most frequently expressed concern.

Patients with ulcerative colitis have been shown to have better QoL scores than patients with Crohn's disease - none of whom were treated with HPN (385), thus illustrating the impact of the underlying disease.

From the above text it is clear that there have been many efforts to evaluate QoL in people treated by HPN. The most influential factors appear to be age, underlying disease (243), social circumstances (392), opiate dependence (393) general malnutrition (395), length of time on HPN (405), ability to work (392;396) and perhaps the presence of a stoma (399;404). Price (386) proposes that the earliest stages of HPN are the most difficult. QoL of HPN patients has been compared to patients with functional and anatomical short bowel syndrome, type II diabetes and congestive cardiac failure. However there seems to be agreement that end stage renal disease is an appropriate comparison.

1.14.4 Longitudinal QoL Data

Most studies have reported QoL data from a single time point (250;327;388;392;393;396). Jamieson et al (395) used the NHP to evaluate HPN patients for up to 4 years. They saw an improvement in QoL scores in group 1 (BMI < 20), 5 of which were receiving HPN. Another study asked patients to retrospectively compare their QoL before and after HPN dependence, which can not be classified as a longitudinal QoL study. In 2002 Malone reported longitudinal QoL in HPN patients on two occasions 3 years apart (414). It is unclear whether her sample was of 12 or 13 HPN patients. SF36 scores did not change over the time period. There has been no longitudinal QoL study which specifically identifies patients newly discharged on HPN.

1.15 QoL in Adult Pseudo-Obstruction

People suffering with pseudo-obstruction may require nutritional input including oral nutritional supplementation, enteral and parenteral nutrition or a combination of these therapies. Symptoms can be episodic or continuous and include abdominal pain, distension, constipation and vomiting, and this may have an impact on QoL.

A literature review revealed 3 abstracts and 2 original communications related to this area of research.

In 2000 Iwarzon et al (415) assessed pseudo-obstruction patients self-reported symptoms, functional status and health related QoL (HRQoL) using the Gastrointestinal Symptoms Rating Scale (GSRS), the sickness impact profile (SIP), the Swedish QoL questionnaire (SWED-QUAL) and the psychological general wellbeing index. They found that compared to healthy controls, pseudo-obstruction patients had poor QoL and poor general well being. There was a strong correlation between severity of symptoms and QoL, the main determinants of poor QoL being abdominal pain, indigestion and diarrhoea. In 2004 Chambers et al (416) used the SF36 and HADS to identify that 23 pseudo-obstruction patients had significantly lower role physical (RP) and general health (GH) scores when compared to a healthy population, and that clinically significant levels of anxiety and depression levels were seen in 20% and 17% of the population respectively. In 2006

Keller et al published an abstract which used the SF36 to evaluate QoL in 6 patents with pseudo-obstruction. They found that QoL was decreased in pseudo-obstruction patients when compared with healthy controls.

Iwarzon et al published a further article in 2009 which compared health related QoL and symptom severity between 28 patients with pseudo-obstruction and 26 with enteric dysmotility (ED) using the GSRS, SWED-QOL and SIP questionnaires (417). Patients with pseudo-obstruction reported a greater impairment of functional status and HRQoL than did patients with ED. Abdominal pain severity was found to be the only independent predictor of HRQoL.

The latest report which discusses QoL in pseudo-obstruction states that near total small bowel resection caused an improvement in QoL in six patients, however it was not stated how QoL was evaluated, merely that it improved (418).

1.16 QoL in Paediatric HPN

Initial research into the effects HPN had on lifestyle were concerned with the restoration of productive life (for example returning to school or participating in physical/peer group activities) and growth and development (see table 1.7), the general consensus being that HPN allowed infants to have normal psychological development and lifestyle. QoL was acknowledged in many of these papers, but no formal assessment was undertaken. In 1990 Ricour et al evaluated QoL using medical and psychological interviews, however they fail to report the results in any detail, but state that HPN provides a remarkable improvement in QoL (200). Howard et al (1995) was the first group to recognise that a more sophisticated QoL assessment of either the patient or a close family member was required (176).

The 1997 systematic review of HPN (170) highlighted the lack of proper QoL assessments in paediatric studies. Further reviews come to the same conclusions that there was a distinct lack of studies which assessed the QoL in paediatrics (221;247;248).

Candusso et al published 2 papers looking at outcome and QoL in paediatric HPN, however, disappointingly they did not even attempt to study the QoL of children on HPN but merely state that long term patients suffered from psychological disability, that QoL is not easy to determine (287), and that QoL still needed to be evaluated (4).
The first study which tried to evaluate both the child's (by proxy) and caregivers QoL was published in 2003. Engstrom et al used an un-validated HPN questionnaire, the Child Behaviour Checklist (CBCL) and the Interview Schedule for Social Interaction (ISSI). Results from 20 families suggest that the children on HPN (mean age 7, range 3-15 years) were significantly less socially competent and that they had more psychological and emotional problems when compared to (Swedish) population norms – more specifically, demanding a higher level of attention, expressing distress about being alone and often crying. Their parents also felt they were anxious, shy, sensitive, they often showed bad temper and emotions that fluctuated rapidly (205).

In 2005 a French group used the Qualin questionnaire for children <3, the Auquei questionnaire for children age 3-11 years, and the OK.ado questionnaire for adolescents, and found that QoL of HPN dependent children is not different from that of healthy children. They postulate that the lack of difference is because the children on HPN have not had a healthy life with which to compare, and they are accustomed to the HPN (231).

Table 1.7: Studies of QoL/Functional Status in Paediatric HPN

Author	Year	Title	QoL Assessment	Outcome
Dudrick (126)	1969	Can intravenous feeding as the sole means of nutrition support growth in the child and restore weight loss in an adult? An affirmative answer	Clinical parameters	Normal growth and development and faster restoration to productive life
Filler (127)	1969	Long-term total parenteral nutrition in infants	Clinical parameters	Reduced length of hospital stay and acceptable growth
Strobel (177)	1978	Home parenteral nutrition: results in 34 pediatric patients	Ability to pursue normal peer group activities	The majority attended full time classes and resumed relatively normal lives and had an improved state of general well being
Strobel (129)	1979	Home parenteral nutrition in children with Crohn's disease: an effective management alternative	School attendance and participation in peer group activities	Improved QoL on HPN
Byrne (179)	1979	Home parenteral nutrition	Clinical parameters and participation in peer group activities	All patients showed sufficient growth, school attendance improved and patients were able to lead relatively normal lives at home
Farmer (419)	1979	Prognosis of Crohn's disease with onset in childhood or adolescence	Medical interviews	2/3^{rds} considered they were functioning in a suboptimal state of health
Cannon (180)	1980	Home parenteral nutrition in infants	Neurological examinations, sequential developmental assessments and Gesell evaluations	Appropriate developmental milestones can be expected during the 1st 2 years of HPN

Continued…Table 1.7: Studies of QoL/Functional Status in Paediatric HPN

Author	Year	Title	QoL Assessment	Outcome
Wolfe (174)	1983	Experience with home parenteral nutrition	Ability to function as outpatients	Depressive symptoms were common and satisfactory growth and development was maintained on HPN
Ralston (223)	1984	Somatic growth and developmental functioning in children receiving prolonged home TPN	Sequential developmental assessments and Gesell evaluations	Majority of children experienced adequate somatic and behavioural growth over the first 3 years of life
Farmer (420)	1985	Long-term follow-up of patients with Crohn's disease. Relationship between the clinical pattern and prognosis	Telephone interviews	It is not clear how many of these were paediatric cases. QoL tended to be suboptimal among operated patients and was better in those with segmental involvement of the colon/ileum.
Ricour (35)	1985	Enteral and parenteral nutrition in the short bowel syndrome in children	None stated	Patients QoL is near normal on HPN
Amarnath (421)	1987	Home parenteral nutrition in chronic intestinal diseases: its effect on growth and development	Medical notes/interviews	Psychological problems were noted. All patients had improved stamina and general sense of well being.
O'Connor (422)	1988	Intellectual and Perceptual-motor performance of children receiving prolonged home total parenteral nutrition	Wechsler Preschool and primary scale of intelligence, Beery Buktenica developmental test of visual motor integration	Children had average intelligence with perceptual-motor delays and some problems of attention

Continued…Table 1.7: Studies of QoL/Functional Status in Paediatric HPN

Author	Year	Title	QoL Assessment	Outcome
Ricour (200)	1990	Home parenteral nutrition in children: 8 years of experience with 112 patients	Medical and socio-psychological interviews	Remarkable improvement in QoL
Weber (83)	1991	Short-bowel syndrome in children. Quality of life in an era of improved survival	None stated	Excellent growth, development and QoL
Bisset (199)	1992	Home parenteral nutrition in chronic intestinal failure	Griffith's mental development scale and the Wechsler pre school and primary scale of intelligence	Patients were able to grow and develop normally after discharge home
O'Hanrahan (225)	1992	The Role of HPN in the Management of Intestinal Failure. Report of 400 Cases	School attendance and development	Patients appear to enjoy a satisfactory lifestyle.
Candusso (218)	1995	Long-term HPN in children	None specifically stated	Parents and patients all had behaviour disorders (depression)
Leonberg (423)	1998	Long-term growth and development in children after HPN	Neurologic examination, assessment of expressive and receptive language, auditory memory and visual motor function	Development was normal, some discrepancies were seen between language and perceptual motor performance
Candusso (287)	2001	Home parenteral nutrition in children: outcomes and quality of life	None	Long term patients suffer from psychological disability

Continued…Table 1.7: Studies of QoL/Functional Status in Paediatric HPN

Author	Year	Title	QoL Assessment	Outcome
Candusso (4)	2002	Outcome and quality of life in paediatric home parenteral nutrition	None	Disability especially if the treatment was started at birth
Engstrom (205)	2003	Psychological distress associated with HPN in Swedish children, adolescents and their parents: preliminary results	HPN questionnaire (not validated), CBCL and ISSI	More psychological and emotional problems than population norms
Gottrand (231)	2005	Satisfaction in different life domains in children receiving HPN and their families	Qualin questionnaire, the Auquei questionnaire and the OK.ado questionnaire	QoL of HPN dependent children is not different from that of healthy children
Colomb (249)	2007	Long-term outcome of children receiving HPN: a 20 year single centre experience in 302 patients	None stated	Repeat hospitalisations has a serious impact on QoL

Table 1.7 illustrates the lack of proper validated methods of determining QoL in children. One of the important measured outcomes of HPN has been QoL. These studies have revealed that HPN reduces QoL for recipients to the same extent experienced by patients on home dialysis for renal failure (404)

A major aim of providing parenteral nutrition in the home setting is to minimise morbidity and maximise survival and QoL (2). Clinicians understand that HPN is a complex and time consuming procedure and attempts have been made to allow patients (and carers) a more normal lifestyle during the day, for example, feeding at night (over 10-14 hour periods) (177).

1.17 Telemedicine

The term 'telemedicine' is a composite word derived from the Greek 'tele' meaning 'at a distance' and the word 'medicine' which itself derives from the Latin 'mederi' meaning 'to

heal'. Telemedicine has numerous definitions, Murphy (424) first coined the term in the 1970s, referring to health care delivery in which physicians examine distant patients through the use of telecommunications technologies. The European Commission's health care telematics programme defines telemedicine as: "rapid access to shared and remote medical expertise by means of telecommunications and information technologies, no matter where the patient or relevant information is located."

There are many other definitions ranging from simple one-line statements to full reports. The World Health Organisation offers a holistic definition of telemedicine: "The delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities". Broadly defined, telemedicine is the transfer of electronic medical data (i.e. high resolution images, sounds, live video and patient records) from one location to another. This transfer of medical data may utilize a variety of telecommunication technologies, including, but not limited to: ordinary telephone lines, ISDN, ATM, the Internet and satellites.

The idea of performing medical examinations and evaluations through a telecommunication network is not new.

1.17.1 History of Telemedicine

There are differing views about the origin of telemedicine. Some say that telemedicine came about with the introduction of the telephone. Dr Alexander Graham Bell used his invention when he was feeling ill to call his friend Watson for help. Some believe that the early stages of telemedicine actually began in the 1920s when several countries offered offshore medical advice from hospitals to their fleet of trade ships by using the Morse alphabet. Others say that telemedicine originated not long after the introduction of television.

The initial idea behind telemedicine was, and is, to overcome time and distance barriers. From inception, the focus has been on physical diagnosis and prognosis. Physical diagnosis usually requires visual information, hence one needs a device that would enable the physician to 'see' the patient.

An example of an early application of telemedicine involved the Papago Native American tribe in the late 1950s. Space Technology Applied to Rural Papago Advanced Health Care (STARPAHC) (425) delivered health care to residents living in remote areas of the Papago Indian Reservation in Arizona. This was a joint effort between Lockheed, the National Aeronautics and Space Administration (NASA), and the US Public Health Service. The project lasted about 20 years.

In 1959, another attempt at telemedicine was made at the University of Nebraska. Dr. Cecil Wittson was in charge of the first two-way video link between the institute and Norfolk State Hospital which was 112 miles away. They used this link for education purposes, as well as consultations between specialists and general practitioners. In 1971, the institute was linked with three other facilities.

Telemedicine was utilised in the early 1960's when NASA first put men in space. Physiological measurements of the astronauts were telemetered from both the spacecraft and the space suits during NASA space flights. These early efforts were enhanced by the development of satellite technology which fostered the development of telemedicine.

NASA was not the only one to experiment with the integration of telecommunications systems into the practice of medicine. During the late 1960s and early 1970s, others were also experimenting with telemedicine.

The first telemedicine system in which there was a regular interaction between physicians and patients was installed in Boston in 1967. A radiologist set up a diagnostic 'shop' in the Logan airport health centre. Physicians were invited to bring X-rays and patient data. The X-rays were illuminated by an ordinary light box, scanned by a black and white television camera and the images transferred to a video monitor in Massachusetts General Hospital's (MGH) radiology department. The physician could discuss the case with MGH

radiologists via an ordinary telephone line. These early experiments demonstrated that it was possible to undertake remote diagnosis through interactive television and that the transmission of medical data (e.g., X-rays) could be accomplished successfully without any significant loss of information in terms of its quality and detail.

Most of these projects used some form of video (black-and-white television, colour television, slow-scan transmission) to complement the most basic unit of telemedicine equipment, the telephone.

The use of telemedicine grew out of a need to provide medical diagnoses for patients in remote areas who were unable to travel. There also was a need to help small towns by providing doctors with technology that would allow them to keep abreast of advances in medicine and to consult with other physicians.

From these beginnings, the interest in telemedicine has continued to grow. Today, telecommunications networks are being developed to transmit information about patients to doctors and information from doctors to patients, faster than ever before, and eventually from any location. These same networks can be used to provide access to on-line patient records and medical libraries, to facilitate communications among medical specialists around the country, and make available standardised medical information and insurance data more readily. Telemedicine technology is advancing and will continue to do so. Although much of the more sophisticated technologies such as virtual reality are still expensive, the cost of some technologies is dropping, so that telemedicine should become more affordable to more people, regions and countries than ever before.

1.17.2 Clinical Uses of Telemedicine

A Pubmed search in April 2004 using the subject heading “Telemedicine” retrieved approximately 6300 citations dating back to 1974. When this search was repeated in 2008, over 10,000 citations were returned illustrating how this technology is a rapidly expanding field. Telemedicine is and has been used in a growing number of medical specialties such as: cardiology, homecare, radiology, emergency care, surgery,

dermatology, psychiatry, oncology, pathology, ophthalmology, haematology, ENT, renal medicine and pre-hospital care.

The technology has improved and the cost of equipment has decreased in the past ten years, resulting in an increase in the number of telemedicine research projects and increase in the scope of those projects. The Telemedicine Information Exchange (1997) (http://tie.telemed.org/default.asp) lists over 130 telemedicine research sites.

At present there is limited nurse led published evaluation of nursing initiatives with telemedicine in the UK compared to other countries i.e. USA and Australia.

The use of providing patients a telephone contact with the primary HPN centre has been shown to minimise separation and disruption in families, discouraged a feeling of total dependence on, or insecurity of being at home, and encouraged a sense of self sufficiency and ability to carry on in a normal environment even in the face of HPN adjustments or complications (13).

1.18 Recruiting Controls in Paediatric Populations

Obviously when undertaking a clinical study it is important to have a control population with which to compare to the diseased population. However identifying and recruiting controls in paediatric studies can be problematic. Selection bias occurs when controls are not a representative sample of the population from which the case emerged. The potential for sample bias can be minimised by maximising the probability that a representative sample will be selected ideally by random sampling or some other kind of unbiased sampling (426). There is very little in the literature on recruiting paediatric controls, even though this can be the weak point in a paediatric study design. We hoped to ask parents with children on HPN to rate their own and their child's QoL by proxy. We therefore needed to recruit a control population with which we could compare these results.

This subject was discussed in detail at the 2003 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) QoL working group. Historically, in the UK it is very common for studies to recruit paediatric controls from

the children of people who work at the hospital, from children who have another (sometimes less severe) illness or from children from GP practices in the same geographical area as the case group (Dr. A Thomas, personal communication, August 2003). There was consensus that each of these methods of obtaining a paediatric control population resulted in the introduction of some degree of bias.

The aforementioned methods of recruiting paediatric controls do not take into account socio-economic status, education (parental and child), social grade or geographical area. For example, the parents of children who work at the hospital may live in a different area, may contain a higher percentage of people who have attended further or higher education, and potentially have a higher income than a case population. Also a hospital worker may become somewhat over-sensitised or desensitised to certain types of illness if they are dealing with it on a daily basis. Trying to compare a case group with children who have another illness can also be inappropriate as the illnesses may not be comparable with respect to pain, disruption of daily living, social stigma and the amount of care and treatment required. Recruiting paediatric controls from GP practices in the same geographical area as the case group considers geographical area, but none of the other social or educational parameters.

Using any of these methods to recruit a paediatric control population would thus result in some sort of bias. There is little evidence to support other methods of recruitment, so a consensus was reached at the 2003 ESPGHAN QoL working group to devise a novel approach for recruiting a paediatric control population. It was discussed in great detail, and decided that the parent (or main carer) of the case child would be asked to nominate or suggest a healthy control family. More specifically, a family who they felt were the same in numbers of children, ages of children, who lived nearby or in the same area and had a similar income. Examples to be provided to the case family included - the family of someone who went to the same school or nursery as their child, the family of a friend of their child, a sibling or close friend or colleague's family who have children of similar ages as their own.

It was considered that the parents with a child on HPN might feel embarrassed or might not want to ask another family to undertake something of this nature. For this reason a blank envelope with all the information for the control family was sent to the case family. If they did not want to pass this on to a nominated family, then they did not have to.

It was hoped that this approach would minimise selection bias as the case family would be suggesting a control family that they felt in some ways were similar. Generally, it is more probable that siblings or friends or families who live in a similar area, whose children attend the same schools, are more likely to be matched on one or more social, economic or educational parameters and are to some extent representative of the case population. As this is a novel way of recruiting a paediatric control group the type and amount of bias would be unknown. There is always a danger that the case families could fail to nominate a family, or nominate an inappropriate family (which would be difficult to detect), or that the control family would be unresponsive. Moreover, this type of control sample selection is not random or unbiased. But in the absence of a better or more robust alternative method of selecting controls, I decided to test this approach, firstly to see if it was accepted by the case and control families and secondly to identify if it caused any problems or obvious confounding variables. This method is new and therefore requires validation.

2.0 Aims and Objectives

The objectives of the 3 studies presented were to investigate and compare aspects of QoL in adult patients who require HPN, in adult patients who have chronic intestinal pseudo-obstruction and in carers of and children receiving HPN.

The specific aims of the studies were to:

- Recruit adult patients being newly discharged on HPN, in order to define and quantify longitudinal changes in SF36 scores, EQ5D scores and HAD scales at the time of discharge home on HPN and over the first year after discharge home and to compare this with a normative population. To document prospectively the number of visits to hospital outpatient clinics (nutrition, or other), the number of admissions to hospital and days in hospital during the course of the first year of treatment. To compare the results of the above in patients receiving standard care and those in contact with a nutrition nurse specialist (NNS) via telemedicine.
- Contact patients diagnosed with pseudo-obstruction with the intention of identifying a cross sectional measurement of SF36 scores, EQ5D scores and HAD scales. To document method of nutritional intake and other clinical indications. To compare the above QoL results with the clinical features and a normative population.
- Identify families with a child under 5 years old on HPN with the purpose of determining cross sectional measurements of the functional status of the child (FSIIR), the GHQ28 score, WOCQ score and HAD scale of the main carer of the child and to asses the level of family functioning. To compare the above measurements with a case controlled group.

3.0 Materials and Methods

3.1 Hypothesis Testing

3.1.1 Study 1 QoL in Adult HPN and Telemedicine

Null Hypotheses: SF36, EQ5D and HAD scores in patients on HPN are not affected by clinical parameters, do not alter over the first year on HPN and are the same as the general population. Telemedicine has no effect on the QoL of patients on HPN

Alternative Hypotheses: SF36, EQ5D and HAD scores in patients on HPN are affected by clinical parameters, change over the first year on HPN and are different from the general population. Telemedicine has an effect on the QoL of patients on HPN.

3.1.2 Study 2 QoL in Pseudo-obstruction

Null Hypothesis: SF36, EQ5D and HAD scores of pseudo-obstruction patients are not affected by method of nutritional intake and other clinical factors and are not different to a normative population.

Alternative Hypothesis: SF36, EQ5D and HAD scores of pseudo-obstruction patients are affected by method of nutritional intake and other clinical factors and are different to a normative population.

3.1.3 Study 3 QoL of Children on HPN and their Carers

Null Hypothesis: There is no difference in WOCQ, FAD, GHQ28, HAD and EQ5D scores in parents who have a child on HPN compared with parents who do not have a child on HPN. FSIIR scores are not different in children who do or do not receive HPN.

Alternative Hypothesis: There is a difference in WOCQ, FAD, GHQ28, HAD and EQ5D scores in parents who have a child on HPN compared with parents who do not have a child on HPN. FSIIR scores are different in children who do or do not receive HPN.

In order to meet the aims and objectives of the studies, consenting patients or their parents who were eligible were recruited into one of three studies.

3.2 Study 1: QoL in Adult HPN and Telemedicine

3.2.1 Study Design

This was a multi centred, randomised, controlled, longitudinal (prospective) trial. Patients were recruited by the Nutrition Nurse Specialists (NNS) in the participating centres before discharge. When the patient was discharged the NNS contacted the trial coordinator.

All patients received standard care and follow up according to his/her centres usual protocol. The control group had telephone links with the NNS, whilst the telemedicine group had telemedicine contact with the NNS at the specified time points:

- Weekly for the 1st month
- Fortnightly for the 2nd month
- Once monthly for the next four months
- At least once every 3 months for the remainder of the study

Subjects were advised by the NNS that after discharge they would receive a telephone call from the trial coordinator on 4 occasions where they would be asked a series of QoL questionnaires. Questionnaire data collection was carried out two days after discharge home and then 6, 12 and 18 months from discharge. At the end of the first year all patients in the trial were offered telemedicine as an incentive for them to participate in the trial and further data was collected for a maximum of one year for each patient.

HPN patients were randomised to receive telemedicine or telephone follow up from each centre, therefore I was interested not in the direct effect of the specific (but various) underlying diseases which result in IF and the need for HPN, but in the overall QoL of these patients as a group and how this was influenced by time and telemedicine contact with the base hospital. Our intervention was not designed to affect physical symptoms caused by either the underlying disease or the HPN and therefore a disease specific questionnaire was not used. The majority of studies which have measured QoL in HPN patients have used the SF36 (79;327;393;396;398-402) and these studies have illustrated that the SF36 is able to detect significant differences in this population when different parameters are compared. Using the SF36 allowed comparisons with other adult HPN

series. EQ5D and HAD were employed to supplement and if possible amplify our understanding of any changes observed.

3.2.2 Inclusion/Exclusion Criteria

The inclusion criteria were any consenting patient that was starting home parenteral nutrition de novo and who were being sent home with Calea (a private homecare company). Calea was providing and funding a telemedicine service, at a time when other homecare companies were not consistently offering this service. The exclusion criteria were failure to consent, using another homecare company for supplies, being under 18 years old, unprepared or unable to use telemedicine and unable to respond to questionnaire by telephone.

3.2.3 Randomisation

A centre specific four block randomisation process, restricted by centre, was applied, which was only enacted after a signed consent form was received.

3.2.4 Telemedicine Installation

Telemedicine requires installation of an ISDN line. In practice this took between 1 and 3 weeks to be completed. After the line had been installed, a videophone was delivered to the patient who was given a tutorial on how to use the equipment. Each of the participating HPN centres had telemedicine installed at the beginning of the study. Initially a PC with a camera and conferencing device was provided, but it was felt the added benefits of the PC would be a confounding factor. The protocol was changed so that a videophone was to be provided instead. None of the trial patients received a PC, but some of the HPN centres did.

3.3 Study 2: QoL in Pseudo-obstruction

3.3.1 Study Design

This was a single centred observational, cross sectional study. A detailed retrospective analysis of the case notes by 2 investigators (Dr. Emma Grieg and Professor Jeremy Powell-Tuck), identified cases of pseudo-obstruction based on radiological, manometric

and histological reports. Eligible patients were contacted by letter to explain the study and invite them to participate. Written consent was obtained. Researchers then contacted patients to answer any further questions about the study and arrange an appointment for the telephone questionnaire.

Information from the patient's notes were recorded and put into a database by Alison Chambers which allowed comparison of the QoL data with clinical features, manometric, histological and radiological findings.

The SF36 was chosen to measure QoL as pseudo-obstruction patients often need nutritional support including EN and HPN. There are studies using the SF36 which have measured QoL in HPN patients (79;327;393;396;398-402) and enterally fed patients (327;427;428) and these studies have illustrated that the SF36 is sensitive enough to detect significant differences in these populations when different parameters are compared. As with study 1, EQ5D and HAD were employed to supplement and if possible amplify our understanding of any changes observed.

Age

To date there are no published studies which have identified age as a predictor of QoL in pseudo-obstruction patients. Evidence was sought from the literature to see if age had any impact on QoL in HPN and enteral nutrition, as many patients suffering with pseudo-obstruction receive this type of nutritional support. In 1997 Richards and Irving observed significantly lower scores in physical functioning, social functioning and emotional role SF36 domains in HPN patients who were older than 45 years old (396). Jeppesen et al observed that HPN patients below the age of 45 scored significantly better on the overall, physical and psychosocial dimensions of the sickness impact profile (404). Patients on enteral nutrition who were younger than 45 years old have been found to have significantly higher SF36 physical functioning scores (428). In light of the above studies, the pseudo-obstruction data was subdivided and compared in patients who were older and younger than 45 years old.

Diarrhoea

One of the symptoms consistently recorded in the medical records was the absence or presence of diarrhoea. However this was not an objective measure and purely reflected the patient's perception of diarrhoea. GI function exhibits a wide range of normal objective parameters and can be highly variable overtime both within and between individuals. The term diarrhoea means different things to different people and is commonly used by the general public to describe a change in bowel habit, but the extent to which this term correlates with objective measures of diarrhoea is not clearly known. The vast majority of anecdotal reports of diarrhoea are actually transient fluctuations in stool consistency and are of little or no clinical significance (429). Moreover, previous studies have revealed a discrepancy between recalled and recorded bowel habits (429-431). It may be misleading to rely on patients recall as it is often imperfect (432) and people tend to exaggerate bowel frequency (433). In light of these findings, our patient's perception of suffering with diarrhoea was not compared to QoL outcomes.

Full thickness small bowel biopsy:

Full thickness specimens or biopsies of the small intestine were obtained laparascopically or during surgical intestinal resection. Full thickness biopsies only were included in this analysis to allow examination of the smooth muscle layers and nerve plexuses by Professor Joanne Martin who has a specialist interest in this area of intestinal pathology. Multiple levels of the sections were stained, to include haematoxylin and eosin, elastic van Gieson, alpha smooth muscle immunohistochemistry, periodic Schiff, CD45 and CD117 immunohistochemistry. Categorisation into "normal", "myopathy", "neuropathy", "non specific partial actin deficiency", or "abnormal indeterminate" was done blind to manometric diagnosis.

Intestinal Manometry:

24 hour ambulant intestinal manometry was performed by a perfused tube placed through the pylorus using radiographic control. This uses 5 sensors in the proximal small bowel with contractions identified by computer and artefact eliminated. Diurnal, nocturnal and meal-related patterns of the migrating motor complex (MMC) were studied in patients in

whom drug therapy, particularly opiate analgesia and smooth muscle relaxants were stopped or curtailed prior to investigation. Patterns may be seen which can be divided into being suggestive of (a) neuropathy in which the contractions are uncoordinated but of normal amplitude and (b) myopathy in which contractions are coordinated but of low amplitude. Interpretation of the traces was principally computer-based using automatic comparison of the patient's recordings with a control database in respect of cycle length, duration, median amplitude, frequency of contractions in phases II and III and also velocity of phase III. Temporal analysis also included day cycles, night cycles, contraction incidence and cluster frequency. In addition subjective assessment by two experienced observers - Professor David Wingate and Professor David Evans, following international guidelines contributed to an overall broad categorisation into myopathy, neuropathy, abnormal indeterminate or normal. Final categorisation was done blind of histopathological diagnosis by Professor David Evans.

Gastric Emptying

Rates of gastric emptying were measured using gamma scintigraphy and/or electrical impedance tomography following previously described techniques (434-436).

Radiological assessment

This relied on the recorded radiologist's reports in each case. The principal abnormality sought was small bowel dilatation in the absence of mechanical obstruction.

3.3.2 Inclusion/Exclusion Criteria

Inclusion criteria were any adult patient who had presented to Bart's and the London NHS Trust Intestinal Failure Clinic between its inception in 1989 and 1st May 2005 who had been diagnosed with pseudo-obstruction. Exclusion criteria were patients who failed to consent, who were unable to respond to the telephone questionnaire or who were diagnosed with secondary pseudo-obstruction due to scleroderma or HIV.

3.4 Study 3: QoL of Children on HPN and their Carers

3.4.1 Study Design

This was a multi centred observational, cross sectional, case control study. Subjects and their families were identified by the paediatric NNS in each participating centre, who provided the trial coordinator (Alison Chambers) with their contact details. An information pack was then sent inviting them to participate in the research project. If the family was interested in participating they were asked to complete a family information sheet, consent and assent forms and send them back to the researcher in a stamped addressed envelope. The families were then contacted within 1 week to arrange a convenient time to complete the telephone questionnaire. During this telephone interview the researcher fully discussed the process by which controls were recruited and asked the main carer if they could nominate a control family. After the telephone questionnaire 2 postal questionnaires were then sent to the family. See appendix 8 for organisation chart.

In order to obtain families of similar age, background and geographical setting, controls were recruited from families recommended by the subject's families. The researcher sent a letter to the subject's family which they were asked to pass to another family who they felt they were similar to in age, number of children, social class and race and who lived nearby. This contained an information pack explaining the study and inviting them to take part in the research. If the control family were interested in participating they were asked to complete the family information sheet, consent and assent forms and send them back to the researcher in a stamped addressed envelope. After receiving the completed forms the families were contacted within 1 week to arrange a convenient time to complete the telephone questionnaire, after which 2 postal questionnaires were sent to the families. See appendix 8 for organisation chart.

Several measures were used to identify QoL and functional status in this population. It is hypothesised that having to care for a child on HPN can be stressful and the WOCQ was used to try to assess the coping strategies used by these carers. The GHQ28 was chosen for its use as a screening questionnaire, as we hoped to identify any psychiatric disorders present in carers of children on HPN. The FSIIR has particular strengths for the

measurement of health status of children with chronic physical conditions – who are not disabled and is thus appropriate for use in children on HPN. Finally, the FAD was used to try to detect any effects on the whole family of having a child on HPN.

3.4.2 Inclusion/Exclusion Criteria

The inclusion criterion for the subjects was any consenting parents or guardians caring for a child who has been receiving HPN for greater than 6 months. Exclusion criteria were failure to consent and the inability to respond to either the telephone or postal questionnaire. The only specified exclusion criteria for the control families were if they had a child with a chronic illness.

3.5 Administration of Questionnaires

In all 3 studies, telephone questionnaires were administered by Alison Chambers (trial coordinator) not involved with the patients' care. In study 1, a week before the next questionnaire was due a letter was sent out reminding patients of the date and time of the telephone call. If a patient was unable to be contacted the trial coordinator made 3 attempts at contacting the patient by telephone and if unsuccessful sent a further reminder. In study 3 postal questionnaires were sent to the participating families, who were asked to complete them and return them in the stamped addressed envelope.

3.5.1 Analysis of Questionnaires

Once the questionnaire scores from all 3 studies had been collected, the raw data was entered into specially designed Microsoft Excel spreadsheets. From the raw data, QoL scores were calculated. The SF36 normative data is gender, culture and age specific. Normative data was adjusted to match our population by taking mean age and gender scores from published general population data (359).

3.5.2 Medical Record Data Collection

At the end of each study the trial coordinator visited hospitals which had recruited patients to the trials. Full medical records were analysed in an attempt to determine factors contributing to developmental outcome. Clinical information obtained from medical records included diagnosis, date of admission and discharge from the HPN

centre, date of CVC insertion, presence of a stoma, use of opiates, no. of outpatient clinics, no. of inpatient episodes and days, no. of CVCs and whether they were still receiving HPN. Patients were contacted and asked to confirm hospital visits where possible.

3.6 Participating Centres

The subject populations in studies 1 and 3 consist of patients recruited from 15 UK centres. All major centres in the UK who provide an adult and or paediatric HPN service were approached to participate in the studies. Several centres declined to be in the studies for two main reasons. Firstly because they felt their HPN population was too small. Secondly because the NHS Trust had contracts with specific HPN providers not involved with study 1.

Table 3.1: Centres Which Participated in the Research Projects

Centre	Geographical Area	Study
Hope Hospital	Manchester	Study 1
Saint Marks Hospital	Harrow	Study 1
The Royal London Hospital	London	Study 1,2 &3
Leeds General Infirmary	Leeds	Studies 1&3
Dudley NHS Trust	Birmingham	Study 1
The John Radcliffe Hospital	Oxford	Studies 1 & 3
Ninewells Hospital	Dundee	Study 1
Leicester Royal Infirmary	Leicester	Study 1
Queens Medical Centre	Nottingham	Study 1
Booth Hall Hospital	Manchester	Study 3
Birmingham Children's Hospital	Birmingham	Study 3
Yorkhill Hospital	Glasgow	Study 3
Great Ormond Street Hospital	London	Study 3
Bristol Royal Hospital For Children	Bristol	Study 3
University Hospital of Wales	Wales	Study 3

3.7 Ethical Consent

The system of obtaining ethical consent in the UK is constantly evolving and changing. Ethical consent was obtained for 3 separate research projects (over 5 years), but because consent was sought at different time points, the processes and committees differed slightly.

For study 1- the HPN, telemedicine and QoL study, multi centred ethical approval was obtained from the London MREC (Multi-centred Research Ethics Committee), and

ethical authorisation was acquired from the Local Research Ethics Committees (LREC) at each participating centre. Subjects were approached and interviewed by a member of the nutrition team, and asked if they would like to participate in the study. Information sheets and consent forms were provided. On agreement the consent form was signed and faxed to the trial coordinator. Upon receiving the consent form, patients were randomised within 24 hours.

With the pseudo-obstruction study (study 2), ethical approval was also obtained from the London MREC, although this was not a multi centred study. Patients were introduced to the study by letter and asked to return a signed consent form if they wanted to participate. A telephone questionnaire was arranged then a subsequent audit of the case notes was translated into an anonymous database which allowed comparison of the clinical features with radiological, manometric and histological findings.

The paediatric HPN study (study 3) required COREC (Central Office for Research Ethics Committee) ethical approval which was obtained from the South West MREC (Multi-centred Research Ethic Committee). LREC (Local Research Ethic Committee) and R&D approval was then acquired for each participating centre. Participating centres then sent the researcher contact details for all the families who were eligible for inclusion. Subjects were then sent a letter and information sheets and consent forms were provided. Upon receiving the consent form, the parent or guardian was contacted within 1 week to arrange a time for the telephone questionnaire.

In all 3 research projects, confidentiality was maintained by allocating patient record numbers known only to the trial coordinator and patients were not provided any compensation for participation in these studies.

3.8 Comparison and statistical analysis

The 2 types of data represented in these studies are:

- Categorical (qualitative) ordinal data, e.g. HAD Scale and EQ5D

- Numerical (quantitative) continuous data, e.g. SF36, WOCQ, FAD and GHQ28

Questionnaire data is derived data. This is an arbitrary value, but can be treated as continuous variables (437).

The SF36 manual provides estimates of sample sizes necessary to detect differences between two groups in SF36 average scores, and to detect differences overtime within one group (longitudinal measures).These estimates assume alpha = 0:05 and power = 80%. The SF36 outcome score is from 0-100, and the sample size needed to detect a difference of 20 points (on a 100 point scale) varies between each domain see table 3.2.

Table 3.2 Sample Size Needed to Detect a Difference of 20 Points in Average SF36 Scores

	Sample size needed to detect a difference of 20 points	
SF36 Domain	**Between 2 Groups**	**1 Group Over time**
Physical functioning (PF)	22	15
Physical role (RP)	47	30
Bodily pain (BP)	23	15
General health (GH)	17	11
Vitality (VT)	18	12
Social functioning (SF)	21	14
Emotional role (RE)	44	28
Mental health (MH)	14	9

All statistical data analysis was done using Intercooled STATA 8 package

3.8.1 Study 1 – QoL in Adult HPN and Telemedicine

Comparisons were made between SF36 and EuroQol scores and HAD to determine if the results were substantiated. The control population was compared with those who received telemedicine upon discharge. It would have been ideal to further subdivide our study population by opiate use, presence of stoma, employment status, and gender, however the

limited number of subjects prevented this and analysis would not be meaningful. The HPN population was compared to normative population data (359).

If you expect the variability to be similar in two groups, then provided you have a reasonable number in each group (paired analysis), t-tests will be sufficiently accurate. The data does not have to be normal. If the data is significantly not normal and the sample size is less than 15 then it is possibly better to use a non parametric test. However the non parametric tests require the groups to have similar shaped distributions (Statistician Enid Hennessy, personal communication 20th April 2009). We expected the variability to be similar in two groups and had a reasonable number in each group therefore it was assumed that t-tests would be sufficiently accurate. The statistical tests applied were t-tests and Pearson correlations. The level of significance was set at $p<0.05$.

Pearson Correlations: measures the degree of association between 2 variables.
SF36, HAD, and clinical outcome data were compared using paired and unpaired t-tests as appropriate. Pearson χ^2 testing was used for EQ5D data.

3.8.2 Study 2 – QoL in Pseudo-obstruction

The same statistical analysis was applied as in the first study.

3.8.3 Study 3 – QoL of Children on HPN and their Carers

Data Distribution

Non parametric tests (sometimes referred to as distribution free tests or rank methods) are particularly useful when the sample size is small (so that it is impossible to assess the distribution of the data) and when the data are measured on a categorical scale (HAD & EQ5D). But non parametric tests are generally wasteful of information and consequently have less power of detecting a real effect.
In fact, scores on the 8 subscales were probably not all normally distributed because of the small size of the sample.

Wilcoxon signed-rank test was chosen as the sample size is small (12 matched pairs) and we were therefore unable to determine the distribution of our data. The Wilcoxon signed-rank test was chosen over the sign test as it takes into account the ranks of the data as well as the sign of the data and is thus more powerful (437).

Obviously the protocols for sending a patient home on HPN differ between centres and to a large extent depend on the experience of the centre. For this reason centres are not identified for comparative purposes in publication as this was a worry voiced by some of the smaller centres when planning these studies.

4.0 Results

4.1 Study 1: QoL in Adult HPN and Telemedicine

4.1.1 Study Sample Characteristics

A total of 30 subjects were recruited to the study from 8 out of the 9 centres involved between March 2001 and June 2003. Fourteen subjects remained on HPN for one year. Reasons for HPN being discontinued were death (7), bowel adaption (8), and one subject was lost to follow up. Acute diagnosis was classified as short bowel syndrome occurring suddenly or a result of bowel infarction, chronic intestinal disease was classified as Crohn's disease or pseudo-obstruction. Functional short bowel was defined as the functional loss of extensive segments of small intestine so that absorptive capacity was severely compromised. Clinical information was collected for 29 of the subjects, and we were unable to obtain a full medical history for one subject as their notes were lost in the post. The mean age was 46 years old, 19 (63%) had a stoma, 15 (50%) used opiates and 11 (37%) had an acute onset of disease resulting in the need for HPN.

Table 4.1: Study 1 - Population Diagnosis

Diagnosis	Total	Telemedicine	Control
Ischaemic bowel disease	6	4	2
Crohn's disease	6	3	3
Functional short bowel	4	1	3
Pseudo-obstruction	3	3	0
Radiation enteritis	2	0	2
Volvulus	2	0	2
Adenomatous polyposis	1	1	0
Neuropathy	1	1	0
Raynauds phenomenon	1	1	0
Sclerosing encapsulating peritonitis	1	1	0
Syringomyelia	1	0	1
Ulcerative colitis	1	0	1

4.1.2 Differences between the Telemedicine (TM) and Control Groups

The subjects in our sample were randomised into 2 groups – standard care follow-up (control), or standard care follow-up with telemedicine. Table 4.2 shows the demographic and clinical differences between the 2 groups.

Table 4.2: Study 1 -Differences between the TM & the Control Group

	TM (%)	SD	Control (%)	SD	P Values
Male	8 (50)	0.5	5 (35)	0.5	0.448
Female	8 (50)	0.5	9 (65)	0.5	0.448
Mean Age	44	12.7	46	13.8	0.752
Presence of Stoma	11 (73)	0.5	8 (57)	0.5	0.377
Opiate Use	9 (60)	0.5	6 (43)	0.5	0.374
Acute diagnosis	4 (27)	0.5	7 (50)	0.5	0.381

The telemedicine group contains a higher number of patients with stomas (p=0.377), a greater percentage of opiate users (p=0.374) and a lower percentage of subjects with an acute diagnosis (p=0.381) when compared to the control group although these differences were not significant. The mean time of hospitalisation over the first year was 31.7 and 26 days which corresponds to 9 and 7% of the year for the telemedicine and control group respectively.

It was postulated that telemedicine might facilitate earlier initial discharge from hospital by perhaps providing an enhanced method of communication. The patients receiving telemedicine had a mean of 75 days, whilst the control group had a mean of 65 days as an inpatient before their initial first discharge, although a t-test comparison indicated that this difference was not significant (p=0.29). Further analysis suggested that there was no significant correlation between the number of days as an inpatient before initial discharge and opiate use (p=0.33) or acute diagnosis (p=0.99). Patients who had a stoma spent on average 27 more days in hospital before initial discharge than those without a stoma (although this was not significant - p=0.073), which may explain why the telemedicine

group (which contained a higher number of patients with a stoma) had a longer mean number of inpatient days before their initial first discharge.

4.1.3 Comparison of QoL Scores between HPN Population and Normative Data

The study population was compared to adjusted normative population data.

Table 4.3: Comparison of Mean Total HPN Cohort SF36 Scores with Normative Data

Domain (n)	HPN (SD)	Norms (SD)	P value
PF 2 Days (27)	33.7 (26.6)	86.7 (6.2)	< 0.001
PF 6 Months (21)	57.9 (32.1)	86.1 (6.7)	< 0.001
RP 2 Days (27)	3.7 (9.1)	85.8 (6.7)	< 0.001
RP 6 Months (21)	33.3 (42.8)	85.1 (5.5)	< 0.001
BP 2 Days (27)	38.6 (27.5)	77.9 (4.7)	< 0.001
BP 6 Months (21)	45.9 (29.7)	77.1 (5.1)	< 0.001
GH 2 Days (27)	35.5 (22.3)	70.6 (3.3)	< 0.001
GH 6 Months (21)	33.1 (23.2)	70.4 (3.2)	< 0.001
VT 2 Days (27)	28.3 (21.2)	57.8 (2.5)	< 0.001
VT 6 Months (21)	43.3 (24.8)	57.6 (2.5)	0.015
SF 2 Days (27)	21.3 (27.7)	82.4 (2.1)	< 0.001
SF 6 Months (21)	47.0 (33.3)	82.3 (2.0)	< 0.001
RE 2 Days (27)	49.4 (44.7)	85.6 (2.2)	< 0.001
RE 6 Months (21)	71.4 (43.8)	85.2 (2.3)	0.164
MH 2 Days (26)	57.2 (20.5)	72.0 (2.6)	0.001
MH 6 Months (22)	65.5 (23.7)	72.2 (2.6)	0.200

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

Upon initial discharge, in all domains except Role Emotional and Mental Health the study population had significantly lower scores (indicating lower QoL) than the normal population. RE and MH however were not significantly different at 6 months post initial discharge.

Table 4.4: Comparisons of Mean Total HPN Cohort HAD Scores with Normative Data

HAD Score	HPN Mean (SD)	UK Normative Data Mean (SD)
Anxiety 2 Days	7.1 (3.9)	6.1 (3.8)
Depression 2 Days	6.3 (3.5)	3.7 (3.1)
Total Score	12.5 (7.0)	9.8 (6.0)
Anxiety 6 Months	7.0 (4.5)	6.1 (3.8)
Depression 6 Months	6.5 (4.2)	3.7 (3.1)
Total Score 6 Months	9.4 (8.6)	9.8 (6.0)

The HAD scale authors (372) suggest cut offs for anxiety and depression. Raw scores of <7 indicate no case, scores between 8–10 identify mild cases, 11 – 15 moderate case, and 16 or above severe cases. According to these guidelines the HPN mean population scores imply the anxiety and depression scores are not clinically relevant.
Crawford et al (374) also suggest the addition of the anxiety and depression scores to yield a Total Score which measures general psychological distress. This tends to produce higher scores, however, there are no published cut offs for the total score.

It was not possible to obtain normative data adjusted to our population therefore I was unable to determine the significance of differences seen.

Table 4.5: Comparison of EQ5D Scores between TM, Control & Normative Data

EQ5D Domain	% of TM group reporting any problem	% of Control group reporting any problem	Mean % of Study Population reporting any problem	% of Normal Population with any Problem
MB 2 Days	71.4	76.9	74.1	18.4
MB 6 Months	50.0	61.5	57.1	18.4
SC 2 Days	57.1	30.8	44.4	4.2
SC 6 Months	25.0	30.8	28.6	4.2
UA 2 Days	92.9	92.3	92.6	16.3
UA 6 Months	75.0	69.2	71.4	16.3
PD 2 Days	78.6	69.2	74.1	33.0
PD 6 Months	75.0	84.6	81.0	33.0
AD 2 Days	42.9	46.2	44.4	20.9
AD 6 Months	50.0	38.5	42.9	20.9

Table 4.5 shows the percentage of the study population who had any problem with Mobility (MB), Self Care (SC), Usual Activities (UA), Pain and Discomfort (PD) and Anxiety and Depression (AD). Results from UK normative data (376) are also shown.

There is little difference between the TM and control group in any of the domains, and comparison with the normative data reveals the HPN population report more “any problem” scores in each domain than normal.

At both 2 days and 6 months the HPN populations report more moderate or extreme problems than the normal population.

4.1.4 Longitudinal QoL Scores

Repeated measures were taken at several time points throughout the duration of the study, allowing the observation of time on QoL scores. QoL scores were measured at 2 days, 6, 12 and 18 months post discharge. By one year the sample size had become too small to

allow for meaningful analysis, so statistical analysis was performed between 2 days and 6 months. As no significant differences in SF36 scores or any other parameters measured between the telemedicine and control group were observed, the two groups were pooled together for the remainder of the analysis.

Table 4.6: Comparison of Mean Total HPN Cohort SF36 Scores between 2d & 6m

SF36 Domain (n)	2 Days (SD)	6 Months (SD)	P Value
PF (19)	38.9 (25.5)	50.5 (31.7)	0.021
RP (20)	3.75 (9.2)	30.0 (41.0)	0.011
BP (20)	37.3 (28.5)	39.5 (27.6)	0.592
GH (20	35.6 (22.5)	31.5 (22.4)	0.184
VT (20)	28.75 (21.6)	41.0 (24.0)	0.059
SF (20)	22.5 (29.1)	44.4 (31.8)	0.006
RE (20)	48.3 (46.5)	68.3 (44.5)	0.055
MH (20)	57.4 (22.3)	64 (24.5)	0.117

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

The data indicates that there is a significant increase in PF, RP and SF. There is a trend for QoL to be higher at 6 months in VT and RE. This increase in QoL is not observed in MH or BP.

Table 4.7: Comparison of Mean Total HPN Cohort HAD Scores between 2d & 6m

	2 Days (SD)	6 Months (SD)	P Value
Anxiety	7.1 (4.2)	7.0 (4.5)	0.940
Depression	6.2 (3.7)	6.5 (4.2)	0.690
Total Score	12.5 (7.0)	9.4 (8.6)	0.033

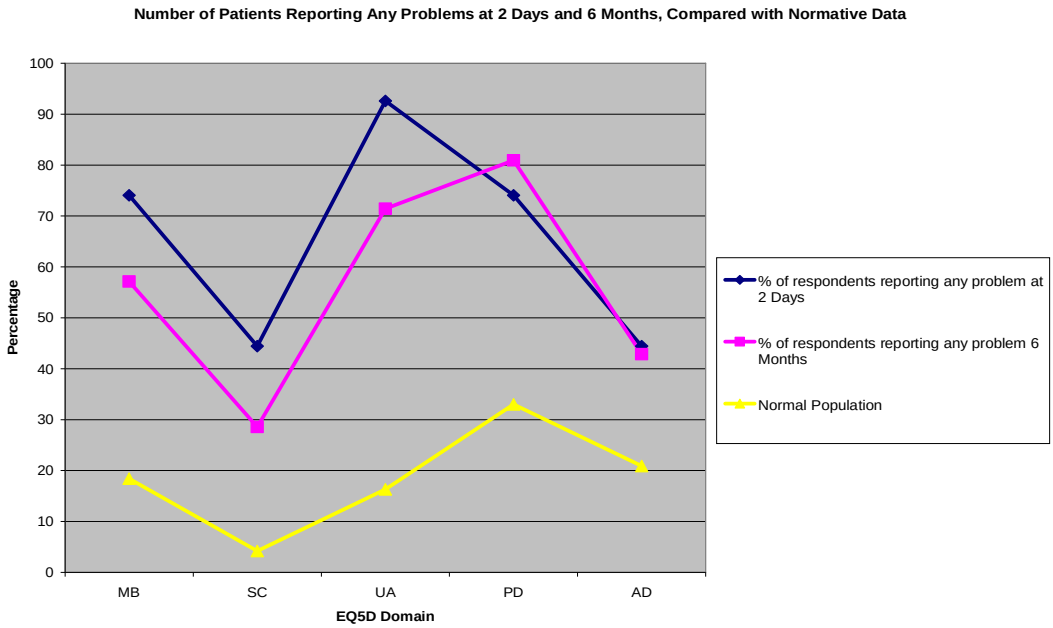
There are no significant changes in anxiety or depression over between 2 days and 6 months of HPN therapy. There is a significant reduction in Total HAD score (p=0.033) indicating a reduction in psychological distress between 2 days and 6 months.

Table 4.8: Comparison of Total HPN Cohort EQ5D Scores between 2d & 6m

	% of respondents reporting any problem at 2 Days	% of respondents reporting any problem 6 Months	% of Normal Population reporting any problem
MB	74.1	57.1	18.4
SC	44.4	28.6	4.2
UA	92.6	71.4	16.3
PD	74.1	81.0	33.0
AD	44.4	42.9	20.9

Key: MB=Mobility, SC=Self Care, UA=Usual Activities, PD=Pain and Discomfort, AD=Anxiety and Depression

Figure 1: Percentage of HPN Patients Reporting Any Problem at 2d & 6m Compared with Normative Data



I was unable to analyse the EQ5D in the same way as the SF36 and HADS, because the normative data is expressed differently and it was not possible to apply standard tests of hypothesis. However the graphical representation clearly shows that in all domains (except pain and discomfort), the number of HPN patients reporting any problems (either moderate or extreme) reduces over the first 6 months of HPN and is starting to approach the normative data values. It would be of interest to see if this continues or stabilises over an extended period of time.

4.1.5 Comparison of SF36 Scores by Opiate Use, Acute Diagnosis, Presence of a Stoma and Use of Telemedicine

Student t test comparisons of SF36 scores between those who do and do not use opiates, between those who had a stoma and between those who had an acute or chronic onset of disease were performed.

Table 4.9: Comparison of Mean Total HPN Cohort SF36 Scores by Opiate Use

Domain	Opiate (SD)	N	No Opiate (SD)	n	P Value
BP 2 Days	23.2 (25.9)	14	50.3 (23.4)	12	0.011
BP 6 Months	26.2 (26.6)	12	62.8 (22.4)	9	0.007
RP 6 Months	16.7 (38.9)	12	55.6 (39.1)	9	0.036
VT 6 Months	30.4 (21.3)	12	59.4 (20.1)	9	0.006
SF 6 Months	32.3 (27.4)	12	66.7 (31.3)	9	0.015
MH 6 Months	55.3 (24.2)	12	77.3 (18.3)	9	0.035

Key: BP=Bodily Pain, RP=Role Physical, VT=Vitality, SF=Social Functioning, MH=Mental Health

Not all the analysis is shown, but SF36 scores were significantly higher in those who do not use opiates in RP, BP, VT, SF and mental health.

Table 4.10: Comparison of Mean Total HPN Cohort SF36 Scores by Acute Onset

Domain	Acute (SD)	n	Chronic (SD)	n	P Value
BP 6 Months	66.0 (30.4)	8	33.5 (22.1)	13	0.011
GH 2 Days	52.2 (24.8)	11	26.3 (15.9)	15	0.015
GH 6 Months	56.0 (25.3)	8	21.7 (15.1)	13	0.007
VT 6 Months	60.0 (25.1)	8	34.2 (22.7)	13	0.091

Key: BP=Bodily Pain, GH=General Health, VT=Vitality

Those who were diagnosed with an acute form of intestinal failure had significantly higher QoL scores in BP and GH domains. There was weak a trend for those with chronic intestinal failure to have lower vitality scores.

There were no significances observed between those who did and did not have a stoma. Telemedicine use had no statistically significant impact on SF36 scores.

Table 4.11: Comparison of Mean Anxiety HPN Cohort HAD Anxiety Scores at 2 Days by Opiate Use, Acute Onset, Presence of a Stoma and TM

HAD ANXIETY (n)	Mean Anxiety 2 Days (SD)	P value
Opiate (15)	7.7 (4.7)	0.460
No Opiate (12)	6.5 (3.0)	
Acute onset (12)	5.3 (3.0)	0.031
Chronic onset (15)	8.6 (4.1)	
Stoma (18)	7.3 (4.4)	0.816
No Stoma (9)	6.9 (3.2)	
Telemedicine (14)	7.6 (4.7)	0.530
No Telemedicine (14)	6.6 (3.1)	

Table 4.12: Comparison of Mean Anxiety HPN Cohort HAD Anxiety Scores at 6 Months by Opiate Use, Acute Onset, Presence of a Stoma and TM

HAD ANXIETY (n)	Mean Anxiety 6 Months (SD)	P value
Opiate (11)	7.9 (5.0)	0.369
No Opiate (9)	6.0 (4.0)	
Acute onset (10)	6.1 (4.7)	0.369
Chronic onset (10)	8.0 (4.6)	
Stoma (13)	7.2 (4.8)	0.895
No Stoma (7)	6.9 (4.5)	
Telemedicine (8)	7.2 (4.9)	0.840
No Telemedicine (13)	6.9 (4.4)	

At 2 days, those whose disease onset was chronic had significantly more anxiety than those whose disease onset was acute. This difference has diminished by 6 months.

Table 4.13: Comparison of Mean HAD Depression Scores at 2 Days by Opiate Use, Acute Onset, Presence of a Stoma and TM

HAD DEPRESSION (n)	Depression 2 Days (SD)	P value
Opiate (15)	7.3 (3.2)	0.135
No Opiate (12)	5.3 (3.5)	
Acute onset (12)	5.4 (3.5)	0.169
Chronic onset (15)	7.3 (3.2)	
Stoma (18)	6.6 (3.2)	0.817
No Stoma (9)	6.2 (4.1)	
Telemedicine (14)	6.7 (3.7)	0.520
No Telemedicine (14)	5.9 (3.3)	

Table 4.14: Comparison of Mean HAD Depression Scores at 6 Months by Opiate Use, Acute Onset, Presence of a Stoma and TM

HAD DEPRESSION (n)	Depression 6 Months (SD)	P value
Opiate (11)	8.4 (3.6)	0.052
No Opiate (9)	4.9 (3.9)	
Acute onset (10)	5.9 (4.1)	0.332
Chronic onset (10)	7.7 (3.9)	
Stoma (13)	7.2 (4.3)	0.607
No Stoma (7)	6.1 (3.8)	
Telemedicine (8)	6.4 (4.6)	0.930
No Telemedicine (13)	6.5 (4.1)	

At 6 months there is a trend for those on opiates to be more depressed.

Table 4.15: Comparison of HAD Total Scores at 2 Days by Opiate Use, Acute Onset, Presence of a Stoma and TM

HAD TOTAL (n)	Total HAD Score 2 Days (SD)	P value
Opiate (15)	15.0 (7.0)	0.063
No Opiate (14)	10.1 (6.5)	
Acute onset (12)	10.8 (5.6)	0.229
Chronic onset (17)	14.0 (7.8)	
Stoma (19)	13.1 (7.1)	0.645
No Stoma (10)	11.8 (7.3)	
Telemedicine (16)	12.5 (5.4)	1.000
No Telemedicine (14)	12.5 (8.3)	

Table 4.16: Comparison of HAD Total Scores at 6 Months by Opiate Use, Acute Onset, Presence of a Stoma and TM

HAD TOTAL (n)	Total HAD Score 6 Months (SD)	P value
Opiate (15)	11.9 (9.5)	0.129
No Opiate (14)	7.0 (7.1)	
Acute onset (12)	10.0 (7.3)	0.820
Chronic onset (17)	9.2 (9.7)	
Stoma (19)	9.8 (9.2)	0.843
No Stoma (10)	9.1 (8.0)	
Telemedicine (16)	6.8 (9.1)	0.072
No Telemedicine (14)	12.4 (7.1)	

No significant differences were observed.

Data on patients who extended beyond 6 months were analysed although the sample size was small, however no trends were detected.

4.1.6 Comparison Hospital Contact by Clinical Parameters

Student t tests were used to compare number of outpatient clinics, inpatient episodes, inpatient days, nutrition clinics and CVCs at one year by opiate use, acute diagnosis, presence of a stoma and telemedicine use.

Table 4.17: Hospital Contact at 1 Year by Opiate Use

Variable at 1 Year	Mean opiate (SD)	N	Mean nil opiate (SD)	n	P Value
Outpatient clinics	6.3 (5.1)	15	6.4 (2.8)	14	0.952
Nutrition clinics	4.9 (4.1)	15	4.4 (2.5)	14	0.734
Inpatient days	39.8 (25.6)	14	18.1 (38.7)	14	0.092
Inpatient episodes	3.3 (2.9)	14	1.2 (1.1)	14	0.018
CVCs	2.0 (1.0)	14	1.1 (0.4)	14	0.007

There were no significant differences in outpatient clinic or nutrition clinic attendances or inpatient days between the two groups (table 4.17). Significant differences were found in the number of inpatient episodes and number of CVCs. The group who used opiates had more inpatient episodes and required CVC replacement more often.

Table 4.18: Comparison of Hospital Contact by Acute Diagnosis

Variable at 1 Year	Mean Acute (SD)	n	Mean Chronic (SD)	N	P Value
Outpatient clinics	6.7 (3.0)	12	6.2 (4.8)	17	0.759
Nutrition clinics	5.0 (2.8)	12	4.4 (3.8)	17	0.653
Inpatient days	20.7 (27.0)	12	35.3 (38.1)	16	0.270
Inpatient episodes	1.0 (1.0)	12	3.2 (2.7)	16	0.013
CVCs	1.3 (0.7)	12	1.8 (1.0)	16	0.221

There were no significant differences in outpatient clinics, nutrition clinics or number of inpatient days between the two groups (table 4.18). A Significant difference was found in the number of inpatient episodes. The group who had chronic diagnosis had statistically more inpatient episodes.

Table 4.19: Hospital Contact at 1 Year by Stoma

Variable at 1 Year	Stoma (SD)	n	No Stoma (SD)	n	P Value
Outpatient clinics	5.9 (4.3)	19	7.3 (3.7)	10	0.392
Nutrition clinics	4.6 (3.4)	19	4.8 (3.6)	10	0.871
Inpatient days	32.8 (37.0)	18	22.2 (28.5)	10	0.441
Inpatient episodes	2.6 (2.5)	18	1.6 (2.0)	10	0.287
CVCs	1.7 (1.0)	18	1.3 (0.7)	10	0.230

No significant differences seen.

Table 4.20: Comparison of Hospital Contact by TM

Variable at 1 Year	Mean Telemedicine (SD)	n	Mean Control (SD)	n	P Value
Outpatient clinics	5.7 (4.3)	15	7.1 (3.7)	14	0.392
Nutrition clinics	4.3 (3.4)	15	5.1 (3.6)	14	0.530
Inpatient days	31.7 (37.0)	14	26.3 (28.5)	14	0.681
Inpatient episodes	2.2 (2.5)	14	2.3 (2.0)	14	0.940
CVCs	3.8 (1.0)	14	4.7 (0.7)	14	0.675

Telemedicine had no significant effect on hospital contact.

4.1.7 Multivariate Analysis

It is possible that there are dependent relationships between certain variables. For example opiate use may be dependent on the onset (acute or chronic) of the disease necessitating HPN therapy. Multivariate analysis would be a way to determine and interrogate the presence and or nature of such relationships. However the literature does not provide a consistent answer to the sample size required to perform multivariate analysis. There seems to be a general consensus that to yield statistically meaningful results, the sample size needs to be greater than n=50.

Although the sample size in this study was only n=29, a pair-wise correlation was performed to determine the presence, the strength and direction of any correlations between any 2 variables. The outcome correlation coefficient ranged from -1 to +1, with -1 indicating a perfect negative correlation, +1 indicating a perfect positive correlation, and 0 indicating no correlation at all. However the results indicated no highly positive or highly negative correlations, negating the need for further multivariate analysis. I suggest that the small sample size of the study (n=29) could be a reason that no correlations were observed.

4.2 Study 2: QoL in Pseudo-obstruction

4.2.1 Study Sample Characteristics

A total of 42 subjects were recruited to the study from 60 patients invited (response rate of 70%). Characteristics of the study sample can be seen in table 4.21 Clinical information was collected for 42 of the subjects. Presence of stoma and acute diagnosis were not recorded.

Table 4.21: Study 2: Characteristics of the Study Sample

Variable	No. of Males (%)	No of Females (%)	Total (%)
Gender (n=42)	7 (17)	35 (83)	42 (100)
Mean Age (n=42)	53	42	44
Age Range (n=42)	21-69	19-69	19-69
Opiate Use (n=42)	5 (71)	19 (54)	24 (68)
Oral Nutrition (n=32)	2 (29)	17 (49)	19 (45)
Enteral Nutrition (n=32)	2 (29)	12 (34)	14 (33)
Parenteral Nutrition (n=32)	3 (42)	16 (45)	19 (45)

The majority of our cohort was female, males only representing 17%. The male population was older and contained a higher percentage of opiate users (5 out of the 7 men – or 71%).

Table 4.22: Summary Table of Clinical Investigations/Findings

Clinical Investigation/Event	Findings/Incidence (%)
Histology (n=23)	Normal = 8 (34.8) Actin Deficiency = 5 (21.7) Neuropathy = 2 (8.7) Myopathy = 5 (21.7) Abnormal Indeterminate = 2 (8.7) Actin Deficiency/Neuropathy = 1 (4.4)
Manometry (n=20)	Normal = 3 (15) Neuropathy = 5 (25) Myopathy = 0 (0) Abnormal Indeterminate = 12 (60)
Resection (n=32)	15 (46.9)
Dilated SB (n=32)	10 (31.2)
Delayed Transit (n=15)	11 (73)
Gastric Emptying (n=24)	Delayed = 14 (58.3) Rapid = 4 (16.7) Normal = 6 (25)
Abnormal Oesophageal Manometry (n=8)	7 (87.5)
Hysterectomy (n=28)	11(39.2)
Abnormal Uro-Dynamics (n=6)	4 (66.7)
Urinary Symptoms (n=32)	7 (21.8)

Information regarding clinical investigations and findings were obtained from medical records. Obviously not all patients had all investigations which is why (n) is not constant.

Table 4.23: Current Symptoms of the Study 2 Sample

Current Symptoms	No. of Males (%)	No of Females (%)	Total (%)
Abdominal Pain (n=32)	4 (100)	26 (93)	30 (94)
Vomiting (n=32)	4 (100)	20 (71)	24 (75)
Constipation (n=32)	1 (25)	24 (86)	25 (78)
Bloating (n=32)	4 (100)	17 (60)	21 (66)
Diarrhoea (n=32)	0 (0)	11 (39)	11 (34)
Reflux (n=32)	1 (25)	4 (14)	5 (15)
Dysphagia (n=32)	0 (0)	3 (10)	3 (9)

We were able to obtain information about current symptoms from 32 members of the study population. Due to the fact that the majority of the cohort suffered with abdominal pain, vomiting, constipation, no reflux and no dysphagia, we were unable to statistically analyse the stratified data and correlate it with QoL scores. For example 30 out of 32 suffered with abdominal pain (94%), so we'd be comparing the results of 30 people with the results of 2 people. QoL comparison was only made if n $\geq$10 in each of the groups being analysed.

4.2.2 Analysis of SF36 Scores

Table 4.24: A Comparison of Mean CIIP SF36 Scores with Normative Data

SF36 Domain	Mean CIIP Score (SD)	Mean Normal Score (SD)	t-test p value
PF	44.5 (31.0)	85.8 (5.5)	< 0.001
RP	19.6 (33.4)	85.3 (4.6)	< 0.001
BP	30.2 (25.2)	76.8 (3.9)	< 0.001
GH	27.9 (16.1)	70.2 (2.6)	< 0.001
VT	26.2 (19.3)	56.8 (1.7)	< 0.001
SF	41.5 (28.2)	81.7 (1.4)	< 0.001
RE	68.3 (43.5)	84.6 (1.9)	0.019
MH	60.7 (23.9)	71.1 (2.4)	0.008

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

Highly statistically significant results demonstrate that those with pseudo-obstruction have a poorer QoL than the normal population as ranked by every SF36 domain.

Table 4.25: Comparison of Mean CIIP SF36 Scores by Age

SF36 Domain	Up to 44 years old Mean Score (SD)	Over 45 years old Mean Score (SD)	t-test P value
PF	48.3 (29.6)	40.7 (32.5)	0.432
RP	17.9 (31.8)	21.4 (35.6)	0.733
BP	26.7 (22.0)	33.7 (28.2)	0.375
GH	26.2 (16.3)	29.6 (16.0)	0.502
VT	26.7 (21.0)	25.7 (17.9)	0.875
SF	45.4 (24.6)	37.6 (31.6)	0.376
RE	76.2 (39.6)	60.3 (46.7)	0.241
MH	60.6 (23.8)	60.8 (24.5)	0.980

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

SF36 scores were correlated with age, no statistical differences were found in those older or younger than 45 years old, which is in contrast to the results found from other studies of HPN patients (396;404) and home enteral nutrition patients (428).

4.2.3 Comparison of Clinical Information

Table 4.26: Comparison of Mean CIIP SF36 Scores by Opiate Use

SF36 Domain	Opiate use n=24 (SD)	Nil Opiate Use n=18 (SD)	t-test p value
PF	33.1 (28.2)	59.7 (28.5)	0.005
RP	9.4 (23.1)	33.3 (40.2)	0.019
BP	16.1 (11.2)	48.9 (26.7)	< 0.001
GH	22.9 (12.6)	34.6 (18.1)	0.018
VT	21.3 (18.7)	32.8 (18.6)	0.054
SF	32.5 (26.1)	53.6 (27.0)	0.014
RE	66.7 (45.0)	70.4 (42.6)	0.790
MH	58.0 (24.7)	64.2 (22.9)	0.410

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

Those who use opiates report statistically significant lower levels of physical role, general health, physical and social functioning, and worse bodily pain. There was a trend for those on opiates to have poorer VT scores. Interestingly opiate use does not appear to affect emotional role or mental health.

Table 4.27: Comparison of Mean CIIP SF36 Scores by Oral Nutrition

SF36 Domain	Oral Intake n=19 (SD)	No Oral Intake n=23 (SD)	t-test p value
PF	54.2 (30.4)	36.5 (29.8)	0.065
RP	26.3 (41.2)	14.1 (24.8)	0.244
BP	30.8 (27.8)	29.7 (23.5)	0.886
GH	29.7 (16.5)	26.4 (15.9)	0.515
VT	22.4 (20.4)	29.3 (18.1)	0.248
SF	46.2 (30.0)	37.7 (26.7)	0.334
RE	59.7 (47.9)	75.4 (39.2)	0.249
MH	54.5 (28.9)	65.7 (17.9)	0.131

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

Oral intake does not appear to have any impact on SF36 outcomes, although the data suggests there is a trend for higher physical functioning scores in those who are able to eat.

Table 4.28: Comparison of Mean CIIP SF36 Scores by Enteral Nutrition

SF36 Domain	Enteral Intake n=14 (SD)	No Enteral Intake n=28 (SD)	t-test p value
PF	32.1 (31.1)	50.7 (29.5)	0.066
RP	17.9 (28.5)	20.5 (36.0)	0.810
BP	25.6 (13.9)	32.5 (29.3)	0.410
GH	25.8 (14.9)	28.9 (16.8)	0.557
VT	29.6 (18.7)	24.5 (19.7)	0.419
SF	35.9 (30.6)	44.4 (27.1)	0.364
RE	76.2 (38.0)	64.3 (46.2)	0.411
MH	67.1 (18.6)	57.4 (25.8)	0.218

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

Enteral nutrition does not appear to have any impact on SF36 outcomes, although as with oral intake, physical functioning scores are higher in those who do not require enteral nutrition support.

Table 4.29: Comparison of Mean CIIP SF36 Scores by Parenteral Nutrition

SF36 Domain	PN n=19 (SD)	No PN n=23 (SD)	t-test p value
PF	41.8 (30.8)	46.7 (31.6)	0.616
RP	18.4 (29.9)	20.7 (36.7)	0.832
BP	30.8 (25.8)	29.7 (25.2)	0.886
GH	26.8 (16.4)	28.7 (16.1)	0.708
VT	27.1 (20.1)	25.4 (19.0)	0.784
SF	39.6 (29.0)	43.1 (28.1)	0.698
RE	75.5 (41.3)	62.3 (45.3)	0.337
MH	63.2 (20.0)	58.6 (26.9)	0.545

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

Parenteral nutrition does not appear to have any impact on SF36 outcomes.

Table 4.30: Comparison of CIIP SF36 Scores by Resection

SF36 Domain	Resection n= 15 (SD)	No Resection n=17 (SD)	t-test p value
PF	42.0 (30.1)	47.4 (33.4)	0.640
RP	6.7 (20.0)	38.2 (41.6)	0.010
BP	27.5 (24.2)	35.4 (27.8)	0.400
GH	30.3 (17.9)	30.0 (16.3)	0.960
VT	28.0 (17.6)	29.29 (18.4)	0.930
SF	41.9 (22.0)	43.1 (26.5)	0.860
RE	68.9 (44.5)	85.8 (30.8)	0.080
MH	63.5 (19.3)	65.9 (20.3)	0.890

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

Patients who had undergone a previous intestinal resection reported a significantly worse physical role (RP) and there was a weak trend for them to have a poorer emotional role (RE).

Table 4.31: Comparison of CIIP SF36 Scores by Dilated Small Bowel

SF36 Domain	Dilated SB n= 10 (SD)	No Dilated SB n=19 (SD)	t-test p value
PF	53.5 (27.9)	42.1 (34.3	0.370
RP	35.0 (42.8)	19.7 (34.9)	0.310
BP	40.9 (32.8)	26.4 (22.2	0.170
GH	27.8 (20.7	31.1(16.1)	0.640
VT	35.5 (17.1	29.3(18.4	0.930
SF	56.4 (26.5)	43.1(26.5	0.860
RE	66.7 (47.1)	85.8(30.8)	0.080
MH	68.0 (22.4	65.9 (20.3	0.890

Key: PF=Physical Functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health

Table 4.32: A Summary of Statistically Significant Results/Trends Identified

SF36 Domain	**Oral Intake**	**Enteral Intake**	**Resection**	**Dilated Small Bowel**	**Opiate Use**
PF	*0.065*	*0.066*	-	-	0.005
RE	-	-	*0.080*	*0.080*	-
RP	-	-	-	-	0.019
BP	-	-	-	-	0.000
GH	-	-	-	-	0.018
VT	-	-	-	-	0.054
SF	-	-	-	-	0.014

Physical functioning appears to be the domain most affected by method of feeding. Opiate use has a negative impact on nearly every SF36 domain, but it is postulated that this may be due to the fact that these patients are sicker and have more pain – resulting in the depressed score.

4.2.4 Comparison of CIIP HAD Scores by Clinical Parameters

Table 4.33: Comparison of CIIP HAD Scores by Clinical Parameters

Clinical Parameter	Mean Anxiety Score (SD)	P value	Mean Depression Score (SD)	P value	Mean Total Score (SD)	P value
Male (n=7)	7.9 (5.6)	0.976	9.3 (5.7)	0.473	17.1 (10.6)	0.696
Female (n=35)	7.9 (4.4)		7.8 (4.8)		15.7 (8.4)	
Older than 45 (n=21)	8.6 (5.4)	0.316	7.9 (5.0)	0.853	16.5 (9.7)	0.675
Younger than 45 (n=21)	7.2 (3.5)		8.2 (4.9)		15.4 (7.7)	
Opiate (n=24)	8.0 (4.6)	0.826	9.3 (4.9)	0.049	17.4 (9.1)	0.224
No Opiate (n=18)	7.7 (4.6)		6.3 (4.5)		14.1 (8.0)	
Oral (n=19)	8.7 (5.0)	0.320	8.5 (5.1)	0.573	17.2 (9.5)	0.399
No Oral (n=23)	7.3 (4.2)		7.7 (4.8)		14.9 (8.0)	
Enteral (n=14)	6.9 (4.8)	0.333	7.4 (4.8)	0.571	14.4 (8.6)	0.406
No Enteral (n=28)	8.4 (4.5)		8.4 (5.0)		16.8 (8.8)	
Parenteral (n=19)	7.6 (5.0)	0.679	7.9 (5.2)	0.906	15.5 (8.5)	0.776
No Parenteral n=(23)	8.2 (5.0)		8.1 (4.8)		16.3 (9.0)	
CIP Mean Score (n=42)	7.9 (4.6)	0.016	8.0 (4.9)	< 0.001	15.9 (8.7)	< 0.001
Normal Population (n=1792)	6.1 **		3.7 **		9.8 **	
Resection (n=15)	8.2 (4.5)	0.245	8.5 (5.0)	0.169	16.7 (8.5)	0.163
No Resection (n=17)	6.4 (4.3)		6.1 (4.5)		12.5 (8.1)	
Dilated Small Bowel (n=10)	7.3 (4.5)	0.915	7.4 (4.1)	0.987	14.7 (7.9)	0.949
No Dilated Small Bowel (n=19)	7.1 (4.6)		7.4 (5.4)		14.5 (9.4)	

** = Standard deviation of normative data is unavailable

Opiate users report significantly higher levels of depression. We compared our cohort with normative data from a large non clinical sample (374) and found that those suffering with pseudo-obstruction report significantly (highly) more anxiety and depression.

4.2.5 Comparison of EQ5D Scores with Normative Data

EQ5D scores were analysed and the percentage of the study population who had any problem with Mobility (MB), Self Care (SC), Usual Activities (UA), Pain and Discomfort (PD) and Anxiety and Depression (AD) is shown in table 4.34. Results from UK normative data are also shown (376). I was unable to analyse the EQ5D in the same way as the SF36 and HADS, so the EQ5D is expressed differently.

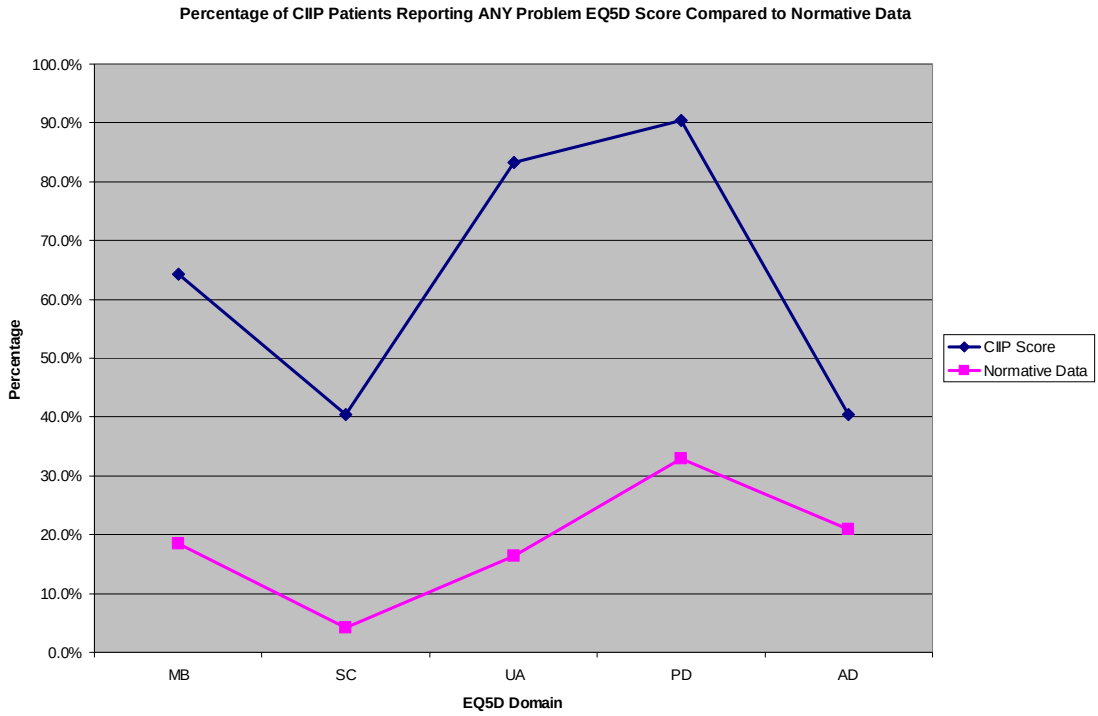
Table 4.34: Comparison of CIIP EQ5D Scores with Normative Data

	Mean Study Population (%)	Normal Population with any Problem (%)
MB	64.3	18.4
SC	40.5	4.2
UA	83.3	16.3
PD	90.5	33.0
AD	40.5	20.9

Key: MB=Mobility, SC=Self Care, UA=Usual Activities, PD=Pain and Discomfort, AD=Anxiety and Depression

Comparison with the normative data reveals the pseudo-obstruction population report on average more “any problem” scores in each domain than the normal population.

Figure 2: Percentage Pseudo-obstruction Patients Reporting Any Problem at 2d & 6m Compared with Normative Data



4.3 Study 3: QoL of Children on HPN and their Carers

4.3.1 Study Sample Characteristics

A total of 23 families were invited to participate in this study. Of those, 12 patients (7 female and 5 male) were recruited from 4 UK centres between September 2005 and April 2007. Twelve control families were recruited in the same time period.

Age at diagnosis was birth for 83% of the cohort (10 out of 12). The only 2 patients not diagnosed at birth were diagnosed at 2 and 7 months. Follow up was recorded for a mean of 4.5 years per child. The number of CVCs required was 50 and there was a mean of 4.1 or median of 3 catheters per child used.

In the case group, reasons for intestinal failure include (n): CIIP megacystis (2), Hirschsprung's (1), hollow visceral myopathy (1), gastroschisis (3), tufting enteropathy (2), protracted diarrhoea (1), phenotypic diarrhoea (1) and short gut syndrome (1). A

stoma was present in 4 and none of the children were classified as being opiate dependent. Full clinical information was collected for 11 of the patients, and limited data was collected for 1 patient.

Table 4.35: Study 3: Characteristics of the Study Sample

Case	Diagnosis	Age	No of Days monitored	IP Episodes	IP Days	OP Episodes	CVCs	Nutrition
1	CIIP Megacystis	4	1757	12	50	23	3	PN + EN
2	CIIP Megacystis	5	2286	22	316	20	5	PN + EN
3	Hirschsprung's	2	850	5	27	6	2	PN + EN
4	Hollow Visceral Myopathy	5	2357	21	30	52	2	PN
5	Short Gut Gastroschisis	5	2331	16	47	41	3	PN + EN
6	Gastroschisis	5	2021	31	267	13	4	PN + EN
7	Tufting Enteropathy	5	2595	32	395	52	10	PN + EN
8	Protracted Diarrhoea	2	955	12	225	33	3	PN + EN
9	Phenotypic Diarrhoea	2	1145	29	209	25	8	PN + EN
10	Tufting Enteropathy	3	1174	-	-	-	3	PN + EN
11	Short Gut Syndrome	1	569	1	12	2	3	PN + EN
12	Gastroschisis	4	1841	11	310	19	4	PN

Table 4.36: Comparison of Case & Control Subjects

Parameter	Case (SD)	Control (SD)	P value
No. Recruited	12	12	-
Mean Age	4 (1.5)	4 (1.8)	1.000
Male	5 (0.5)	4 (0.5)	0.689
Total No. Siblings	6 (1.0)	11 (1.1)	0.338
Mean Age of Main Carer	30 (8.7)	34 (5.6	0.173

The age of the main carer in the case group is older than in the controls, although this was not significant. The control children had more siblings.

4.3.2 Comparison of QoL Scores Between the Case and Control Groups

QoL data was collected for both the case and control group.

Table 4.37: Comparison of WOCQ Raw Scores between Case & Control Groups

WOCQ Domain	Case Mean (SD)	Control Mean (SD)	Wilcoxon Signed-rank
Confrontive Coping	1.5 (0.8)	0.9 (0.5)	0.102
Distancing	0.9 (0.5)	1.3 (0.7)	0.221
Self Controlling	1.3 (0.6)	1.1 (0.5)	0.444
Seeking Social Support	1.7 (0.6)	1.0 (0.5)	0.014
Accepting Responsibility	1.1 (0.7)	1.2 (0.9)	1.000
Escape Avoidance	1.2 (0.9)	0.8 (0.7)	0.356
Planful Problem Solving	1.9 (0.7)	1.5 (0.8)	0.203
Positive Reappraisal	1.3 (0.8)	0.7 (0.5)	0.051

See section: 1.13.7 for information on WOCQ.

The case group used the coping mechanism Seeking Social Support significantly more than the control group. There was a trend for the case group to use the coping mechanism Positive Reappraisal more than the controls.

Table 4.38: Comparison of WOCQ Relative Scores between Case & Control Groups

WOCQ Domain	Case Mean (SD)	Control Mean (SD)	Wilcoxon Signed-rank
Confrontive Coping	13.9 (5.6)	9.8 (5.0)	0.075
Distancing	8.3 (4.3)	16.8 (6.7)	0.028
Self Controlling	11.7 (3.0)	13.8 (6.2)	0.508
Seeking Social Support	16.3 (4.9)	14.2 (9.6)	0.721
Accepting Responsibility	10.2 (4.8)	12.1 (6.9)	0.575
Escape Avoidance	10.1 (6.6)	8.5 (5.5)	0.508
Planful Problem Solving	17.7 (6.6)	17.0 (10.7)	0.879
Positive Reappraisal	11.9 (5.6)	8.0 (6.2)	0.114

The control group used significantly more distancing as a coping mechanism, and there was a weak trend for them to use less Confrontive Coping than the case group.

Table 4.39: Comparison of GHQ28 Scores between Case & Control Groups

GHQ28 Domain	Case Mean (SD)	Control Mean (SD)	Wilcoxon Signed-rank
Somatic Symptoms	7.7 (4.3)	3.4 (2.6)	0.038
Anxiety Insomnia	7.2 (5.2)	3.4 (2.4)	0.012
Social Dysfunction	6.9 (2.8)	5.8 (2.0)	0.360
Severe Depression	2.7 (3.1)	0.4 (0.5)	0.129
Total	24.4 (12.3)	13.0 (5.2)	0.021

The GHQ28 yields sub scores and a total score. The higher the GHQ28 sub scores, the more severe the condition. Total scores can be compared to threshold values, the default cut off indicating a positive psychiatric condition being a score of 23/24. The case group had significantly higher scores in the Somatic Symptom and Anxiety/Insomnia domains. The mean total score exceeds the threshold for a positive psychiatric condition in the case group and is significantly higher than the control mean score.

Table 4.40: Comparison of HADS Scores between Case & Control Groups

HAD	Case Mean	Control Mean	Wilcoxon Signed-rank
Anxiety	8.9 (4.1)	3.8 (3.3)	0.007
Depression	4.8 (3.8)	2.9 (2.2)	0.135

	Case Anxiety	Control Anxiety	Case Depression	Control Depression
No case <7	3	10	9	11
Mild Case = 8-10	4	2	2	1
Moderate Case = 11-15	5	0	1	0
Severe Case = >16	0	0	0	0

The case group to have significantly more anxiety than the control group (p=0.0074) and exceed the level of clinical relevance.

Table 4.41: Comparison of FSIIR Scores between Case & Control Groups

	Case Mean (SD)	Control Mean (SD)	Wilcoxon Signed-rank
FSIIR Score	75.3 (10.5)	96.7 (5.9)	0.003

As would be expected the children on HPN scored significantly lower than the healthy controls.

Table 4.42: Comparison of FSIIR and Transformed GHQ28 Scores

FSIIR (Mean)	GHQ28 (Mean)	**Wilcoxon Signed-rank**
86.0 (13.8)	81.3 (10.9)	0.059

We used Wilcoxon Signed Rank to correlate the GHQ28 and FSIIR and found that there was a nearly significant correlation between the 2 measures. The lower the FSIIR score – the higher the GHQ28 score suggesting that a poor functional status of the child has a negative impact on the general health of the parent.

Table 4.43: Comparison of FAD Scores between Case & Control Groups

FAD Domain	Case Mean (SD)	Control Mean (SD)	Threshold	Wilcoxon Signed-rank
Problem Solving	1.6 (0.5)	2.0 (0.4)	2.2	0.124
Communication	1.8 (0.5)	2.0 (0.2)	2.2	0.502
Roles	2.2 (0.4)	2.1 (0.4)	2.3	0.553
Affective Responsiveness	1.9 (0.3)	1.7 (0.3)	2.2	0.091
Affective Involvement	1.8 (0.4)	1.8 (1.8)	2.1	0.814
Behaviour Control	1.6 (0.3)	1.6 (0.3)	1.9	0.969
General Functioning	1.6 (0.4)	1.7 (0.3)	2.0	0.813

Scores range from 1-4 with 1 reflecting healthy functioning and 4 indicating unhealthy functioning. None of the families (either in the case or control groups) scored above the threshold, indicating no degree of family dysfunction. There were also no significant differences observed between the case and control groups.

5.0 Discussion

The purpose of this thesis was to try and determine the impact that intestinal failure had on QoL. Thus data was collected from 3 distinct population groups: Adult patients newly discharged on HPN; patients with pseudo-obstruction; and children on HPN (and their carers). For each group, separate studies were undertaken involving collection of QoL, clinical and demographic data. This gave a comprehensive set of results from which inference can be drawn.

New definitions of intestinal failure were introduced in 2008 by the Strategic Framework for IF and HPN Nutrition Services for England. This new definition excludes some of the adult patients that have been included in this body of work, who were previously classified as having IF (but did not require HPN); however, the majority of subjects studied suffered with type III intestinal failure and they all had impaired (often severe) intestinal function. From a diagnostic perspective, disease definitions are invaluable and aid clinical practice and epidemiological research. It is important that definitions are updated when necessary in response to research and scientific consensus. Although some of the patients studied were no longer classified as having IF, they still suffered with gastrointestinal symptoms and treatments associated with intestinal failure (for example stoma's, nutritional support, pain and GI motility problems) and the results gained from these individuals are still valuable.

Because the majority of the questionnaires were administered via telephone, missing data was minimal and not significant.

5.1 Development of a Disease or Treatment Specific QoL Questionnaire

Using a generic questionnaire can have the advantages that derived data is comparable with other diseased populations and in many cases, normal population data exist for comparison (as in the case of the SF36). The main disadvantage of using a generic questionnaire is the potential lack of sensitivity to the problems encountered by a specific population. QoL assessments need to include emotional, social, occupational and

physical parameters (438). The generic questionnaires employed in these studies encompass all these factors, but they were not specifically designed for use in patients with intestinal failure. During the period that these studies were undertaken, there were no validated intestinal failure or HPN specific questionnaires available.

Disease or treatment specific questionnaires if designed well and properly validated, are better at focusing on the issues of particular concern to the patients with the disease (439), however there is less scope to compare the results with various other diseases or normal population data.

Designing and validating a disease or treatment specific QoL questionnaire is a highly involved process, and can take time and resources. There are recognised published guidelines on how to develop a QoL questionnaire (440). Briefly, initially there is a literature search to identify issues in the population from which categories and questions are derived. Then interviews with patients and health care professionals pre-test the questionnaire for content validity and acceptability. After this, there are a variety of methods for examining the validity of measurement scales to confirm that the scores appear to be consistent with their intended purpose. The questionnaire should appear to give consistent (reliable) and repeatable results when applied to patients who are believed to be in a stable condition. The scores must be sufficiently sensitive or responsive to be able to detect differences between treatments or patients (439). This process can take a long time to complete, and can involve many editions before it is considered to be acceptable.

Intestinal failure can be the result of a plethora of diseases. Specifically, the HPN population comes from a variety of different backgrounds and medical experiences, which can impact on their perspective and opinion of the treatment. This can make QoL measurement in this population difficult and the sensitivity of generic and disease specific QoL tools used are starting to be questioned in this population (441). This has prompted the development of an HPN therapy specific instrument.

The HPN-QOL is a 48 item questionnaire that focuses on physical, emotional, and symptomatic issues (442). The questionnaire contains functional and symptom scales. The functional scales include general health, ability to holiday (vacation) or travel, coping, physical function, ability to eat and drink, employment, sexual and emotional function. The symptom or problem scales include body image, immobility, fatigue, sleep pattern, gastrointestinal symptoms, other pain, presence or absence of a stoma, financial issues, and weight. Two questions relate to nutrition teams and the availability of an ambulatory pump for infusion of HPN, in which a high score represents a good outcome.

Hopefully the HPN-QOL will provide a more focused assessment of QoL in this population. Ideally QoL needs to be measured periodically or routinely, to identify any patterns over different stages of the treatment or disease. In study 1, SF36 social functioning scores of HPN patients significantly improved over the first 6 months. Future repeated measures with an instrument specifically designed for the HPN population may reveal additional aspects of QoL and health status, that up to now have not been emphasised. It would be a remarkable achievement if this instrument could eventually be incorporated into clinical practice, providing clinicians and health care providers with an enhanced understanding of the social, emotional and symptomatic issues faced by this population.

5.2 Study 1 QoL in Adult HPN and Telemedicine

Thirty patients were recruited who were newly starting on HPN. These patients were prospectively followed over the first year of HPN and their QoL scores were also documented. I also wished to ascertain if telemedicine had an affect on their QoL.

The study population consisted of patients with a broad range of age (22-68) and primary diseases necessitating HPN, enabling me to draw conclusions which represent an array of experiences. The mean percentage of time spent as an inpatient corresponds with previously published data (412).

5.2.1 Comparison of HPN Population QoL with Normative Data

At 2 days post initial discharge the HPN population report significantly lower QoL scores than the normal population in every SF36 domain. This may be due to the fact that patients have gone through a series of initial responses to the loss of intestinal function including denial, sorrow and grief, as reported by Price & Levine (386) and also this could be due in part, to reliance on the pump and the need to be in close proximity to a bathroom (327). The results at 6 months post discharge are in agreement with Richards and Irving (396) in that patients on HPN had significantly lower scores in 6 out of 8 SF36 domains compared to normative data (359). The Mental Health (MH) and Role Emotional (RE) domain scores although lower, were not significantly different from normative data suggesting that either the loss of intestinal function or the initiation of HPN has a more social and physical QoL impact, whilst the mental and emotional state of the patient remains comparable with someone who does not suffer with intestinal failure. The improved results at 6 months perhaps suggest an emotional or mental acceptance and adaptation to the HPN. These findings agree with previously published data (386;396), but also disagree with other researchers who claim QoL is satisfactory in an HPN population (387;388).

There is no doubt that the physical symptoms of intestinal failure can cause considerable and chronic stress. The poor SF36 outcomes in the physical domains may in fact be a disclosure of the severity of the underlying disease, for example pain or weakness. One group reported that quantitatively these are comparable with the quality of life problems related to patients requiring haemodialysis, peritoneal dialysis liver transplant and chemotherapy (392).

Social rehabilitation is often a considered parameter for QoL, and indeed in many of the earlier HPN QoL studies it was the only proxy marker used. QoL has been correlated negatively with distress (anxiety, somatisation, depression), hopelessness and social detachment, and positively correlated with social integration (443).The social aspects of the SF36 aim to assess how well integrated into society a person is feeling, examples include questions about work/usual activities and about visiting friends and relatives. The

results from this study indicate that certainly during the first 6 months social rehabilitation is not fully achieved, but whether this is due to the HPN or the underlying disease remains uncertain. SF36 scores were significantly higher at 6 months compared to 2 days post initial discharge ($p=0.06$), but were still significantly lower than populations norms (359) Time could be a factor and it may be the case that after a protracted period of time an acceptable or better level of social rehabilitation can be achieved.

An attempt was made to compare the HPN population HAD scores with HAD UK normative data (374). However the normative data only supplies an average mean for anxiety, depression and total HAD score. It was thus not possible to obtain normative data adjusted to our population in order to perform analysis. Percentile charts are available, but these yield no interpretable results and were thus not utilised. The UK normative mean scores are marginally lower than our population (indicating less anxiety depression and psychological distress), and while it is not possible to calculate the significance of this, it is possible to identify a trend suggesting that the HPN population suffers with more anxiety and depression than the normal population. The total scale score indicates a higher level of general psychological distress in the HPN group.

The EQ5D questionnaire is a qualitative questionnaire which makes numerical analysis and comparison to a normal population less appropriate. Without exception, when compared to normative data (376) the HPN population report double the amount of moderate or severe problems in every EQ5D domain at 2 days and 6 moths past initial discharge.

The 3 QoL instruments used in this study describe many aspects of the HPN populations QoL in comparison to a normative population. The HAD and EQ5D scales concur that there is increased anxiety and depression. The EQ5D broadly agrees with the SF36 in that both scales demonstrated a reduction in physical functioning including mobility and self care, a reduction in social functioning and usual activities (for example work and social engagements) and an increased level of bodily pain and discomfort. The SF36 and HAD

both detect poorer general health, but are at odds concerning psychological distress and mental/emotional health. The SF36 highlights the relatively satisfactory mental health and emotional role achieved by the HPN patients, whereas the HAD does not. This may emphasise the fact that neither the HAD or EQ5D are sensitive enough or able to assess these parameters considering our SF36 results are in harmony with other published work (396).

5.2.2 Longitudinal QoL Scores

If transition to oral nutrition has not been effected within a two year period, intestinal failure is usually deemed permanent in adults (78). This may influence QoL scores in patients who are disappointed that they are not only on HPN for a limited period. HPN is a complex, high risk therapy for an individual to accept, however we propose that as the patient becomes more experienced, they will feel more at ease and this may have an impact on QoL scores. The data set was too small to analyse at one year, so we compared QoL scores at 2 days and 6 months post discharge, which showed significant improvement in PF, RP, VT, and SF in SF36 domains. Significant differences in the separate anxiety and depression were not detected by the HAD scale, but at 6 months the total HAD score (indicating general psychological distress) was statistically lower than at 2 days which supports the SF36 result.

There is little published data which analyses longitudinal QoL in HPN patients. The majority of current research offers cross sectional measurements. Smith (1993) states that overall a low QoL score was associated with increasing length of time on HPN (392), and Malone reports no change (414). Our data does not support previous findings, but this may be related to our study population being newly discharged and not established on HPN. Jeppesen et al (404) found that patients who had been receiving HPN for less than 2 years scored worse than those with a longer duration of HPN. It may be important to adjust for the length of time on HPN in future HPN and QoL studies.

5.2.3 Comparison of QoL of the HPN Population by Clinical Parameters

Opiate use

SF36 scores were compared between those who do and do not use opiates. At 2 days and 6 months opiate users reported significantly more bodily pain. This is perhaps to be expected, as opiates are used in the management of malignant and non-malignant chronic pain, and it could be postulated that those who require opiates have a more severe disease (and are sicker).

At 6 months opiate users also have less vitality and poorer physical role, social functioning and mental health scores. Again it is unclear whether this is due to opiate use or disease severity. At 6 months HAD depression scores were higher in opiate users. And although opiate users had higher HAD anxiety scores this was not statistically significant.

It would be useful to analyse the data regarding opiate use with and without codeine phosphate as in general codeine phosphate is taken as an anti-motility agent rather than an analgesic and it may not be suggestive of the amount of pain experienced. However due to the data collection process this was not possible. When I collected the data, I recorded if opiates were being prescribed, but not the type of opiate prescribed. This was an oversight in my data collection process.

It would not be ethically appropriate to stop opiate use for medical research to see if this impacted on QoL scores, however this data illustrates that prudence must be shown before prescribing opiate analgesics as they are associated with a poorer QoL. However the quality of life of someone suffering continuous pain will not be high in the first place, and is unlikely to be improved by inappropriately withholding opiates. We do not have data on the effect of prescribing opiates on QoL in such patients.

Richards et al (393) reported the extent to which opiate and benzodiazepine dependence negatively affected outcomes for patients on HPN, with which our data concurs. Van Gossum et al (412) reports that at least a third of their HPN population used opiates. Our

sample had 50% opiate users, which has a negative effect on outcome. It is not surprising that QoL suffers in opiate users. Morale is often low, and anxiety and depression are common. (393)

Acute Diagnosis

A patient's initial response to HPN can be positive or negative depending on their medical circumstances. A patient who develops sudden intestinal infarction for example moves from a state of normality, both of intestinal function and nutrition, to one of intestinal failure and HPN-dependence very quickly. Depending upon medical management, such a patient may never experience malnutrition but will suffer the marked contrast between normality and their newly acquired state. By contrast a patient gradually becoming malnourished and weak as a result of perhaps painful chronic disease might notice the benefits of improved nutrition as HPN is started, but continue to suffer the effects of the chronic underlying disease. A patient with chronic intestinal failure is more likely to start HPN with a greater degree of malnourishment than a patient with acute intestinal failure. Therefore gradual correction of nutritional deficiencies may result in a slow improvement in health and vitality. However their continued intestinal symptoms may tend to negate this effect. If intestinal failure develops slowly the initial response to HPN has been reported to be more positive (277), however this difference in response has been shown to even out after 1 year when confidence in life is restored to all patients (438). Our study did not support these findings and showed that those with a chronic diagnosis suffered with more pain (at 6 months), had poorer general health (at 2 days and 6 months) and had less vitality (at 6 months), presumably as a consequence of their underlying disease. It would be interesting to see if this phenomenon still existed at 1 year and 18 months to see when or if QoL measurements plateau.

Presence of a Stoma

Intestinal failure is often associated with disabilities such as high output stomas causing abdominal distension, vomiting and pain. We subdivided our sample by stoma incidence. In our cohort 63% of patients had a stoma in situ at the time of the questionnaires. The results indicate that the presence of a stoma did not affect QoL in any of the SF36

domains or HAD scale domains. There are 2 main studies with which my data concurs. Richards et al (396) observed no differences in 51 HPN patients SF36 scores between those with and without a stoma. Carlsson et al (399) looked at 28 patients (8 on HPN) with short bowel syndrome and they also found no significant differences in SF36 scores associated with having a stoma. Jeppesen et al (404) found no significant QoL differences in non-HPN patients suffering with anatomical or functional short bowel who had a stoma, whereas in HPN patients with a stoma, QoL was significantly worse. This may be due to the fact that the IBDQ was used to rate HRQoL in this cohort – which may suggest that this disease specific instrument is more accurate at detecting issues surrounding the presence of a stoma and stoma care than the SF36.

Use of Telemedicine

The TM and control group were demographically compared to each other. Some differences between the telemedicine and control group were observed, possibly because randomisation was only restricted by centre. However our sample size was too small to allow for further limitation of randomisation.

There were no differences found between the telemedicine and control groups SF36 or HAD scores at 2 days and 6 months post discharge. From this data it is possible to conclude that telemedicine has no effect on QoL.

An attempt was made to determine the extent of TM use, and how it was utilised, although missing data meant analysis would have been meaningless.

5.2.4 Comparison of Hospital Contact by Clinical Parameters

We found that those who used opiates had significantly more inpatient episodes, more inpatient days (although this did not reach significance p= 0.09) and needed more CVC replacements Those who had an acute diagnosis had significantly less inpatient days and there was a trend towards less CVC replacements. The presence of a stoma had no effect on hospital contact or CVC replacement.

Richards et al (393) found that opiate dependent patients had more episodes of CVC sepsis ($p=0.0007$) and longer periods of inpatient care ($p=0.004$), with which our results broadly agree. The authors do not present an explanation for this. I postulate that opiate users have a more severe underlying disease resulting in the need for additional hospital contact, exposing the HPN patients to the nosocomial environment which has been shown to increase sepsis rates and CVC replacements (176). Currently there are no studies which compare the onset of the disease with hospital visits and number of CVCs. I suggest that those who suffer chronic intestinal failure may be more undernourished and generally sicker (with poorer immunity) which may explain the increased inpatient visits and increased CVC replacements. This information may be useful in the future for budgeting purposes.

5.2.5 Telemedicine Use and Hospital Contact

Dispersion of patient management may have made HPN more universally available, but it has also had the adverse effect of leaving HPN patients more isolated (210). In the UK there are only two nationally funded referral centres, which potentially means patients may find themselves a considerable distance from their specialist centres when they return home (444), some as far as 400km (445), meaning long distances to travel to attend hospital appointments. Indeed it has been reported that patients feel that they need increased accessibility to the PN team to answer their questions or help when they are having problems (210), patients also wish to have more locally available high quality care similar to that which they receive in more remote centres (175). These problems were confirmed and highlighted by a questionnaire study of British people dependent upon HPN conducted by the patients group PINNT in 2001 (response rate 48% of 200) and highlighted at a BAPEN workshop that year (BAPEN workshop on Home parenteral Nutrition: Ensuring Equity of care) Harrogate November 2001 (446).

It was proposed was that telemedicine may have a positive benefit for HPN patients, namely to;

- Reduce the frequency of hospital outpatient visits – by interchanging visits with telemedicine consultations.

- Reduce the number of inpatient episodes – by allowing the visual identification of problems via telemedicine, decreasing the incidence of patients being unnecessarily admitted for only one or two days.
- Facilitate earlier discharge – by providing an enhanced method of communication, any problems could be explained and discussed via the videophone.
- Reduce the number of CVC replacements – by permitting nurses to view the CVC, enabling early detection of problems, reducing the requirement for replacement.

However, our data suggests that telemedicine has no impact (either negative or positive) on outpatient and inpatient visits, post discharge inpatient days, nutrition clinics or CVCs.

Telemedicine is a new technology and patients and nurses alike may feel apprehensive about replacing it for a face to face or outpatient visit. Some of the recurring issues surrounding telemedicine are that of barriers to introduction, risk analysis, economic viability and innovative use of this fast evolving application to healthcare (unpublished Clare Archer). Nurses have reported not feeling confident about making a clinical judgement just by seeing an image of the patient, and will often advise that the patient be admitted anyway. The picture quality is improving as bandwidth increases, but the quality of the image is still an area which could be improved.

While technologies like telemedicine rapidly evolve, it is still the human factors that tend to determine failure or success. Telemedicine has much to offer in the management of patients who are either in a high dependant state needing specialist advice or for those who may live a distance from the specialist centre (447).

We can thus reject the null hypothesis that SF36, EQ5D and HAD scores in patients on HPN are not affected by clinical parameters, do not improve over the first year on HPN and are the same as the general population. We can accept the null hypothesis that telemedicine has no effect on the QoL of patients on HPN.

5.3 Study 2 QoL in Pseudo-obstruction

Pseudo-obstruction is a term which includes many different rare clinical conditions. Our study group was defined by histology, manometry, history of surgical procedures, motility study information and other clinical parameters and symptoms. Forty two subjects who were diagnosed with pseudo-obstruction were asked a series of telephone questionnaires in order to establish their QoL. We achieved a response rate of 70%. Acceptable questionnaire response rates are considered to be in the range of 60–70%, with response rates of over 70% described as very good (448).

The study population consists of patients with an age range of 19-69. The majority of our population was female (83%) and 68% of our cohort were opiate users. Presence of stoma and acute diagnosis were not recorded.

5.3.1 Comparison of Pseudo-Obstruction QoL Scores with Healthy Controls

The pseudo-obstruction population reported significantly lower QoL scores than the normal population in every SF36 domain and HAD scale, indicating that pseudo-obstruction has a negative impact on all aspects of quality of life, which is also supported by the EQ5D results. It is interesting to note that although these results are similar to the HPN cohort (study 1); the pseudo-obstruction patients, who are often clinically regarded as having a major psychological component to their illness, do not report higher levels in SF36 mental health and emotional role scores. Furthermore non-significant small differences only were noted for anxiety and depression between the HPN and pseudo-obstruction cohorts.

5.3.2 Comparison of the Pseudo-obstruction Population QoL Scores by Clinical Parameters

We stratified our pseudo-obstruction population by age, opiate use, oral nutrition, enteral nutrition, parenteral nutrition, diarrhoea, resection and dilated small bowel to try to identify if any of these factors were accountable for the vastly reduced SF36 scores when compared with normative data.

Age and parenteral nutrition had no effect on SF36 and HAD scores. Oral intake had a higher (nearly significant) effect on SF36 physical functioning scores (p=0.06), while there was a trend for enteral nutrition to lower SF36 physical functioning scores (p=0.07).

Opiate use had a significantly negative impact on the SF36 domains physical role, bodily pain, general health and vitality, physical and social functioning. Opiate users also reported significantly more depression (but not anxiety) on the HAD scale. As with study 1, the data collection method was flawed, as only the use and not specific type of opiate use was recorded.

We recorded if any of the pseudo-obstruction patients had had any intestinal resections and found that this had a negative impact on physical role. No differences were seen in HAD scores.

Overall the comparisons of SF36 and HAD scores by small bowel dilation did not yield any statistically significant results, although those suffering with a dilated small bowel tended to have lower mental health scores.

There is only one previous study which examines QoL in pseudo-obstruction (417). They report greater functional impairment and poorer general health in pseudo-obstruction with which our results concur. Interestingly they state that abdominal pain severity was the only independent indicator of QoL. We measured the presence of abdominal pain, but not the severity. Ninety four percent of our cohort had abdominal pain, so when we tried to stratify by abdominal pain, we did not have sufficient numbers in both groups to derive meaningful results.

We can partly accept the null hypothesis that SF36, EQ5D and HAD scores of pseudo-obstruction patients are not affected by method of nutritional intake and other clinical indications. Opiate use and previous intestinal resections negatively affected QoL scores. But we must reject the null hypothesis that pseudo-obstruction patients QoL scores are not different from a normative population.

Obtaining the clinical information was achieved by going through medical notes (often over 9 volumes) and searching the Royal London Hospital's electronic record systems. This was an extremely time consuming process. We believe we managed to extract the majority of clinically relevant data, but this process identified the need for a pseudo-obstruction database, which is currently being developed. Further analysis of the data suggested that for research purposes, more detailed information regarding clinical tests and severity of symptoms would be useful.

5.4 Study 3 QoL of Children on HPN and their Carers

Twelve families who had a child on HPN were recruited from 4 UK centres. Twelve control families were recruited in the same time period. Both groups completed WOCQ, FAD, GHQ28, HAD and FSIIR questionnaires in order to determine the impact that having a child on HPN has on family functioning and QoL.

We attained a response rate of 53%, but due to NHS privacy and confidentiality protocols we were unable to access any further medical or demographic information on the families who declined to participate, and are thus unable to establish the type and extent of bias this created. The study design reduces the possibility of centre bias that may be observed in single centre studies.

The majority of children (83%) were diagnosed with intestinal failure at birth. The only 2 patients not diagnosed at birth were diagnosed before they were a year old. The number of CVCs required were 50 (average CVC life 398 days and 4.1 catheters per child).

5.4.1 Comparison of Case and Control Demographics

A novel, un-validated method of selecting a paediatric control group was used in this study. The families of a child on HPN (interviewed by Alison Chambers) were asked to suggest a control family. All case family carers could think of a suitable family and were happy to pass on the information to the control family. Without exception, all of the control families were willing to participate and data was collected. When I suggested nominating a control family (by telephone after I had finished the questionnaire), there was no resistance or negative reaction to this suggestion. Some of the case carers asked

me to clarify certain points such as the appropriateness of siblings or friends who had moved away. One carer said she had a close friend whose child suffered with cystic fibrosis – and asked if this was ok. I then explained the notion of healthy controls, and she immediately could think of someone else.

From a logistical point of view, this method of recruiting paediatric controls appears to work, and received a positive reaction from both the case and control families. If anything, the control families were more willing to participate as they felt they were taking part as a favour to their friend, relative or colleague. On several occasions the main carer of the control family told me that they would be available for any other questionnaire based studies of this nature, and that they were more than happy to participate.

The recruitment of controls in paediatric studies is always difficult as each method will result in some form of bias including differences in socioeconomic status, geographical area, education level, cultures/religion and family values. Recruiting controls from hospital workers may not be suitable as socioeconomic status, education and desensitising of illness as a result of exposure to the nosocomial environment will probably differ from the cases. Recruiting children with another illness can confound results as the aspects of the illness need to be taken into consideration. Some studies recruit from GP surgeries which mean at least the geographical area will be similar, however many other variables may not be. It is generally considered that where possible, controls should be selected from the same source as cases. The use of neighbourhood controls may ensure that the case and controls are from similar backgrounds (437).

The method we chose to use was discussed and approved at the 2003 ESPGHAN QoL working group meeting and was consensus rather than evidence based. It has not been used in other published studies, and thus data on bias is lacking. However it was felt that by using this method bias would be reduced as the controls would be to some extent a representative sample of the population from which the cases emerged. It is impossible to say if this has been achieved, however parents chose families who they considered to be

similar, both in a social status, numbers and ages of children. A comparison between the case and control groups reveals that the mean age between the children in each group was identical although the parents of the control group were slightly older. In the cases where the geographical area was different, this was due to a sibling of the main carer being chosen. The biggest difference seen was the control children had more siblings. The sample size in this study was small and a bigger study would be required to determine the extent and type of bias created by this method of recruitment.

In this study the main carer of the case family was verbally asked to nominate a control family. A basic script was prepared for this request, and some of the carers needed further clarification of different points. Therefore it is not certain how applicable this method would be in large scale studies where the cases do not have access to an interviewer. This is an important point, because if there is no opportunity for the case subject/family to ask questions, there may be a greater incidence of inappropriate controls being nominated.

To conclude, this novel approach appears to have been fully accepted by both the case and control families. I was unable to identify any obvious confounding variables between the case and control groups. As a method of selecting paediatric controls it did not cause any unforeseen problems. Logistically this method appears to work, but it needs to be validated and interrogated further in a larger sample to highlight the type and/or extent of bias created.

5.4.2 Comparison of QoL Scores between the Case and Control Group

Ways of Coping Questionnaire (WOCQ)

Psychological well-being, social functioning and somatic health are influenced by how individuals cope with stress, not stress per se. Psychological and marital distress caused by caring for a chronically sick child are well described (220). It is postulated that the physical and social complications of providing HPN require an intensive effort, high level problem solving and constant adaptation. By using the WOCQ we hoped to elicit if

the carers with a child on HPN differed in their coping styles from a carer who did not have a child on HPN.

We present both the raw and relative WOCQ scores as the different methods of scoring highlight different aspects, the raw score shows which coping mechanisms were employed, the relative scores show the percentage contribution of each mechanism in coping with the stressful experience.

The results indicate that the carers of a child on HPN significantly seek more social support ($p=0.01$) and use more positive reappraisal ($p=0.05$).

Seeking Social Support is a technical term which describes efforts to seek informational support, tangible support and emotional support. This method of coping is also highly employed in parents caring for a child with cancer (236-238), autism (240) type 1 diabetes (241) and cystic fibrosis (242;449). Engstrom et al found that social interaction in parents caring for a child on HPN, which deals with superficial and simple social contacts (including caregivers of different kinds), is high, whereas attachment, which deals with deeper, emotional relations, is affected. Families tend to be in contact with more people than usual because of the complex medical situation of their child providing less time for deeper relationships with partners, relatives and friends (205) and this may be the case with our cohort.

The ability of the primary care giver to recruit support and child care resources may be crucial to participation in the labour force and in the determination of well being and QoL. Employment (or the decision to quit) may affect not only family finances but also maternal mental health (229).

Positive Reappraisal describes efforts to create positive meaning by focusing on personal growth, enabling parents to draw on their own resources and focus on the positive aspects of their situation. Parents of children with Type 1 diabetes also exercise this coping strategy (241). It is postulated that the main carer of a child on HPN aims to find some

positive elements of the artificial nutrition. This can be illustrated by the response of one mother who implied that although the HPN was demanding, it was better than having her child permanently resident in hospital.

Distancing describes cognitive efforts to detach one-self and to minimise the significance of the situation or stressor. When looking at the percentage contribution of the coping mechanisms, distancing contributes significantly less in parents with a child on HPN ($p=0.02$). This may be due to the fact that HPN therapy requires vigilance on the part of the parent to recognise complications, and the use of distancing as a coping mechanism may put their child at undue risk. The control parents do not have to be prepared for the potentially life threatening situations that can be caused by PN.

As with type 1 diabetes (241), the biggest contribution of coping strategy used by parents caring for a child on HPN was planful problem solving (18%) which describes a major form of problem-focused coping, consisting of rational techniques such as "I knew what had to be done, so I doubled my efforts to make things work". This strategy can virtually be considered opposite to distancing. It implies focus and action on the factor causing the stress, for example coping with pyrexia. Parents are constantly on alert for a crisis because of uncertainty about the child's illness and prognosis (228).

It is interesting to recognise that parents caring for children with autism (240), cancer and HIV (241) scored higher in coping behaviours of distancing and escape, whereas the parents of HPN, type 1 diabetics and cystic fibrosis do not appear to elicit escape avoidance strategies. Perhaps this is because these chronic illnesses are not usually as imminently fatal as cancer or HIV.

A number of mothers caring for a child with CF expressed the belief that they had lost their identity as individuals, and a sense that sacrifices had been endured as a result of their child's diagnosis was frequently voiced (449). Some parents with children suffering from cancer described the feeling that they had had to cope during the active phase of treatment and their own feelings had been set aside. Mothers' appraisals of the strain of

illness-related demands and their confidence in their own ability to deal with these were related to distress (235).

Our results demonstrate that the typical parent of a child on HPN tends to cope by seeking more social support that will usually be from health professionals or people involved with their child's care/health, and by constantly re-evaluating the situation and focusing on a solutions then methodical problem solving.

General Health Questionnaire (GHQ28)

Levels of anxiety and depression are experienced by parents of children with disabilities at home potentially caused by physical and emotional overburden on the carer (228). We used the GHQ28 to detect if any psychological disorders existed.

From our series, the mean total GHQ28 score (24.4) exceeded the threshold for psychiatric morbidity and a further breakdown of the data revealed that a diagnosable psychiatric disorder could be detected in 5 parents (41%) who care for a child on HPN. None of the control families exceeded the threshold, and the mean was significantly lower ($p=0.02$).

Analysis of the subscales revealed that parents with a child on HPN have significantly more somatic symptoms ($p=0.03$) and anxiety and insomnia ($p=0.01$). No statistically significant differences were observed in social dysfunction and severe depression.

Our results are in line with Wong et al (219) who identified the problems faced by parents with a child on HPN. They studied 11 families, 7 exceeded the threshold (Likert score >24) for psychiatric morbidity, and a significant deterioration of social life, family life, sex life and work compared with controls was seen.

Hospital Anxiety and Depression Scale (HADS)

The case group have significantly more anxiety than the control group ($p=0.007$). Using the thresholds it can be deduced that the mean score of the case parents indicates a mild

anxiety. There was no significant difference seen between depression scores. These results concur with the GHQ28 scores in that anxiety is present, but no clinically relevant depression is reported.

The fact that a substantial proportion of the case groups endorsed a number of anxiety items is not surprising. A large scale survey has reported that between 30 and 40% of the general population suffer from anxiety to an extent that would benefit from clinical intervention (374) and it is likely that caring for chronically ill, technologically dependant child could provoke feelings of nervousness. We postulate that high levels of anxiety seen in the case group could be due to the need for parents to be constantly on alert for a crisis.

Functional Status IIR (FSIIR) scores

It has been reported that proxy respondents appear to underestimate the full effect of chronic illness on functional status (360), so we elected to employ the FSIIR in order to enumerate this parameter.

Because children younger than 5 are not able to self report their health or functional status (362) we had no option but to obtain data by proxy. The FSIIR was chosen as it is sensitive to the interface between children who are “normal” and those with severe dysfunction (383), and therefore was applicable to both case and control groups. Studies suggest that parents are better able to rate physical problems (365) and the FSIIR mainly measures behavioural manifestations of illness that interfere with performance (383). As would be anticipated, the children on HPN scored significantly lower ($p=0.0025$) than the healthy controls. It would be expected that children without ongoing medical problems should score higher than children with ongoing medical problems.

A study looking at families of a child assisted by technology found that children had poorer health status (indicated by lower FSIIR scores) and mothers reported a lower mental health SF36 score (229). Correlation between good paediatric glycaemic control and health outcomes in the parents of children with type 1 diabetes has been

demonstrated (450) and associations involving change in symptoms and change in caregiver QoL was significant in parents who cared for children with mild wheeze (451). The design of this study is cross-sectional so we are unable to apply this principle as a function of time/change to our data. However, we compared FSIIR scores and transformed GHQ28 scores from all responders (case and controls) using the Wilcoxon signed-rank method to determine if there was any correlation. The results indicate that the FSIIR scores correlate with GHQ28 scores, although this was not significant (P=0.059) i.e. the poorer the perceived functional status of the child, the poorer the reported general health of the parent.

Family Assessment Device (FAD) scores

Given the intrusiveness and chronicity of HPN therapy, it was postulated that the case families would be at a higher risk of family dysfunction than the control families. Families both affect and are affected by the presence of a chronically ill child (450), however there were no significant differences observed between the case and control groups, and none of the families (case or control) surpassed the thresholds indicating poor family functioning. Other studies of family functioning with a chronically sick child which did not demonstrate differences from controls include type 1 diabetes (450), children with chronic sleep disturbance (452) and paediatric liver transplant (453). A study looking at family functioning in children with food refusal demonstrated that in all FAD subscales the mean score was significantly lower than the control group (454).

5.4.3 Comparison of Clinical Information

Coping with a child's chronic illness is a complex process that can be influenced by the child's gender. It is not known whether, within a family, the mother's and father's use of coping strategies vary as a function of the child's gender. For example, mothers have been reported to be more likely to perceive girls with type 1 diabetes as being more vulnerable than boys (241). There was a fairly equal spread of female and male children in the case group (58% and 42% respectively) which reduces the possibility of gender bias within the case sample. There were a higher percentage of girls in the control group (66%). This may be a confounding factor with respect to analysis.

The average (4.2) and median (3) number of CVCs required per child was much higher than reports from other groups. Ricour et al and Colomb et al report means of 1.25 and 2.6 respectively (200;224). There are 2 reasons postulated for the comparatively high number of CVCs required: 1) Two patients required a total of 18 CVCs (36%) mainly for repeated CVC infections which skewed results. However, removing these outliers from the analysis still resulted in a median of 3 CVCs per child. 2)The vast majority of the children in our cohort were started on HPN shortly after birth and it is known that the risk of CVC infection is higher in children requiring HPN from early infancy than those started after the first year of life (196). The populations in the other studies contain data collected from much broader age ranges with lower risks of CVC complications. It is difficult to assess whether sepsis could be a result of poor training/aseptic technique or could be a consequence of underlying disease.

In our series, only 2 children were exclusively fed by PN. The practice of complimentary enteral feeding can help gut adaptation, reduce the need for PN (4), decrease the occurrence of PN related complications (455) (for example the risk of cholelithiais and liver disease), and allow the acquisition of the social skills of eating (31).

If paediatric HPN continues over 3 years – it is likely to be permanent (82) so according to this rationale 9 out of our 12 children will probably be permanently on HPN. Eleven out of 12 of the children had been receiving HPN for longer than 2 years (Child 11 had been on HPN for 1 year 7 months), so it can be assumed that parents have typically transitioned from the acute phase of HPN management into the phase of long term care. This is of interest as parents of a child on HPN have reported that the initial 8 days to 1 month are extremely trying, but they felt after this they feel much more secure (200). This is comparable to what was conveyed anecdotally by 4 parents when conducting the telephone questionnaires, they felt the first 3 – 6 months were the hardest in terms of adjustment to the HPN.

There was no opiate dependence reported in our series, reducing the use of narcotics has been shown to improve prognostic factors in adults (277). Only one child died during the study period and this was due to the underlying disease.

5.4.4 Inclusion Criteria

This was a case-control, cross-sectional, multi-centred study which was initially conceptualised in 2001. At this time the most relevant data on the epidemiology of paediatric HPN in the UK was the 1998 British Artificial Nutrition Survey (456) which estimated that there were approximately 63 children receiving HPN and the majority of these were under 5 years of age. There was a low incidence of children in all the older age groups (n=<10). By definition, children are evolving and undergoing major changes, including alteration in the level of their dependency and cognitive development, and there is poor agreement on the normal roles and functions of children at different ages (383). Therefore it is difficult to obtain information over a wide age range without using several measures or QoL tools, which means the data obtained will not be uniform in nature or comparable. For this reason we came to the decision to only recruit children who were under 5 years old as we felt there would not be enough children in each of the other age groups to derive meaningful data. Unfortunately by the time we had obtained ethical approval, many of the children were over 5 years old, so could not be included in this study.

Parents had to be sufficiently fluent in spoken and written English to complete the postal and telephone questionnaires and we did not need to exclude any potential participants based on these criteria.

5.4.5 Ethical Approval

One of the major problems faced in the organisation of this study was acquiring ethical approval. Because we intended to recruit from more than 4 centres we were required to obtain COREC approval, which took 11 months from initial application to final approval. After this we were obliged to attain LREC (Local Research Ethics Committee) approval from each centre. The LRECs are supposed to vet the application for any logistical

difficulties that could cause a problem to the NHS trust. However we found that certain LRECs were pedantic about the study principles and design. This process took up to 1 year in some cases. Finally after obtaining COREC and LREC approval we had to seek research and development approval from each trust which again, took up to a year in some cases. Part of the reason this process took far longer than anticipated is because we were undertaking research in children, a group that is considered vulnerable.

We can reject the Null Hypothesis that there is no difference in WOCQ, GHQ28, HAD and EQ5D scores in parents who have a child on HPN compared with parents who do not have a child on HPN and that FSIIR scores are not different in children who do or do not receive HPN. However we must accept the null hypothesis that there is no difference in FAD scores in families who have a child on HPN compared with case controls.

5.5 Limitations of the Study

5.5.1 Study 1 Limitations

This study was limited by time, resulting in the limited period available for both recruitment and follow up of subjects. The duration and overall outcome of HPN varies between countries. A UK study showed only 46% of patients were still on HPN at the end of nine years (321). This highlights a problem for survey follow up, indicating the need for a large sample size at the beginning of the study. The effect of age on HPN therapy needs to be evaluated over a reasonable time period, Howard and Malone found age had a significant effect on all indicators (457). A longer time allocated for obtaining QoL data would allow further analysis of longitudinal HPN QoL data. This study has identified an increase in QoL over 6 months, and it would be interesting to see where this trend goes.

We hoped to recruit a larger sample; however recruitment was limited because of the inclusion criteria. This project was funded by Calea, an HPN care provider, and to be included in the trial the patient had to be discharged with Calea. However some of the centres involved in the trial held HPN contracts with other companies.

The manner in which opiate use was recorded failed to identify the specific opiates that were prescribed. Codeine phosphate is generally taken as an anti-motility agent – and not necessarily as an analgesic. This oversight in data collection meant that this could be a confounding factor that can not be interrogated further.

There are both advantages and disadvantages of using generic questionnaires to measure QoL. This study employed generic questionnaires as we were trying to measure general changes in QoL. A gastrointestinal specific questionnaire would have given us more information about the disease state which may have resulted in more meaningful analysis if used in conjunction with generic questionnaire.

We concentrated on measuring the QoL of the patient, and it may have been beneficial to identify the impact of HPN on the family and carers by encouraging relatives and carers to complete questionnaires. A common social problem to arise in long term HPN is the chronic dependence on a caregiver (250).

Medical records were accessed from 7 different hospitals in the UK. The quality of record keeping varies greatly and although where possible, information was cross checked with the actual patient, the completeness of the data is uncertain.

A treatment specific QoL questionnaire for adult patients on HPN has been developed. The use of this questionnaire should become part of the routine clinical management of all HPN patients (458) and in future HPN QoL studies.

5.5.2 Study 2 Limitations

Our method of recruitment involved sending out letters asking if people would like to participate. This proved to be a successful method; however we were relying on The Royal London hospital medical records which often did not provide accurate or up to date information regarding patient contact details. This means that we are not sure if all patients received the invitation to participate, which could have introduced some selection bias (437).

When it came to stratifying our data, we found that in some cases there were not enough people in each group to yield to statistical analysis. This may be because certain criteria were too broad. For example instead of just recording the presence of abdominal pain, we should have measured the severity of abdominal pain. The use of a disease specific questionnaire would have perhaps endowed us with this information.

The subjective presence or absence of diarrhoea was recorded in this study, but the results were not analysed in this study as patient's perception of diarrhoea does not correlate well with objective measures (429-431). However obtaining a valid gauge of diarrhoea would not have been possible from case note analysis.

Single case studies have merit as a means of generating new ideas or hypotheses or demonstrating areas for future research. But because of the cross sectional design, it is not known if poor QoL continues unabated over time.

5.5.3 Study 3 Limitations

Although this was a multi-centred study, we still only managed to recruit a small sample size of patients. Unfortunately the low incidence of paediatric HPN in the UK makes accrual of large samples difficult. Only 53% of the families invited chose to take part in this project. A much higher referral was seen from Birmingham Children's Hospital and this was probably due to the increased involvement from the nutrition nurse specialists in this centre.

Another shortcoming is that we report only the parent's views of their children's functional status. It would be of great interest to also report the child's own views. This was believed to be impossible with regard to the children's age, and this was certainly true in the younger children. However it may have been possible in the children who were in preschool.

QoL was only assessed in the main carer of a child on HPN, in the majority of cases this being the mother. Caring for a child on HPN affects the whole family and comparing

responses on this impact on both mothers and fathers may have provided some enlightening results.

More detailed information on parents occupation, employment / social and marital status, would have allowed more detailed comparisons with the QoL outcomes. However due to the insufficient statistical power of this study it is not known if this would have offered meaningful analysis.

Since our results are cross-sectional, they do not allow for causal interpretation. It may be useful to examine caregivers QoL at different stages of time such as prior to diagnosis and at intervals while the child is home.

Another potential limitation is that not all respondents returned the surveys in the same manner. The Birmingham caregivers completed the questionnaires in the presence of the nutrition nurse specialist whilst all the other caregivers completed the tools either at home (WOCQ & FAD) and returned them by mail, or over the telephone (GHQ28, HADS & FSIIR). Although mode of administration may have an impact on survey results, with face to face administration yielding higher results, several studies comparing supervised and postal administration have demonstrated these differences to be small (459;460). There is also a possibility that the mothers and fathers completed FAD together while comparing and sharing responses.

5.6 Areas for Further Investigation

5.6.1 Study 1 HPN QoL and Telemedicine

Measurement of QoL using the HPN-QOL (410) would be an exciting area to research in this population. Direct continuation of this study would increase the sample size, thus increasing and adding to the statistical power of the study.

The use of telemedicine did not appear to have any impact on QoL or hospital contact. This may partly be due to both nurses and patients apprehensions about the new

technology and it may be beneficial to look at this and other aspects of clinical management. A study which examined various features and uses of telemedicine including its clinical advantages from both the patient and practitioners point of view would be constructive.

One of the limitations of this study was that the impact of HPN on the whole family was overlooked. The results from study 3 highlight the effect having a child on HPN has on the whole family and it would be intriguing to see if this effect was similar in adults.

HPN is provided by a number of hospitals located throughout the UK, which means obtaining national data can be challenging. The total UK HPN population is not unsubstantial but research in this field can be demanding. Development of an HPN national database may alleviate this situation.

5.6.2 Study 2 QoL in Pseudo-obstruction

Pseudo-obstruction is a condition which has received little attention in terms of QoL research. Our results indicate that further QoL research is warranted which may require multi centred trials. This should include QoL tools which aim to elicit presence and severity of symptoms.

We undertook a one off cross sectional QoL measurement and longitudinal or repeated measurements would depict a more inclusive perspective of the impact pseudo-obstruction has on QoL.

5.6.3 Study 3 QoL of Children on HPN and their Carers

There are very few children on HPN in the UK and thus our sample size was small. Direct continuation of this study would increase sample size and increase statistical power allowing more dissection of how the different types and syndromes of intestinal failure affect QoL. As with the adult HPN population, a national database would facilitate further research.

This study highlighted the problems faced by the carers of a child on HPN and it would be interesting to look at this in greater detail.

This was a cross sectional study which looked at families with a child under 5 years old. Further research could follow these children as they grow older and identify different problems faced at different ages. Older children would also be able to self report their QoL instead of using proxy measurements.

5.7 Conclusions

These studies highlighted some very clear results from which several conclusions can be made.

The adult HPN population have a much lower QoL than the rest of the UK population, which agrees with previous studies. Patients on HPN report increased levels of bodily pain, anxiety and depression, a reduction in physical functioning, social functioning, general health, vitality and satisfactory mental health and emotional functioning. Vitality, physical role, physical and social functioning significantly improve over the first 6 months on HPN. This is new data which needs to be researched further. Anxiety and depression do not change over the first 6 months. Continued research in this field is essential if progress is to be made.

Delaying death or improving QoL are the basic reasons to implement nutrition support, even if there is no hope for a cure. This patient group have to deal with a life changing therapy, and QoL indexes are in the process of being developed and refined which should be specific enough to identify areas that need to be examined.

Pseudo-obstruction has a negative impact on all aspects of QoL indicated by significantly lower QoL scores than the normal population. Age and parenteral nutrition had no effect on QoL. There was a trend for those who did not require nutritional support to have better physical functioning scores, with enteral nutrition causing lower physical functioning scores. As with study one, opiate use had a significantly negative impact on the QoL and

opiate users also reported significantly more depression (but not anxiety). Diarrhoea and small bowel dilation did not yield any statistically significant results. A previous intestinal resection had a negative impact on physical role.

Concern has been expressed that the psychological aspects of treatments are overlooked in the training of paediatric HPN, which concentrates only on technical and logistic competencies required to get children home, with families reporting that more emphasis is placed on medical rather than social problems (202) and it is suggested that we need to look beyond the care of the child to the needs of the mother (449). Our results demonstrate that carers of a child on HPN use different coping strategies from parents who do not care for a child on HPN, seeking more social support and using more positive reappraisal. The contribution of coping strategy also differs, parents caring for a child on HPN use more planful problem solving and less distancing than the control group. A higher level of psychiatric disorder characterised by anxiety is seen although depression does not seem to be clinically significant. Children on HPN have a poorer functional status than those not on HPN, and there is a correlation between level of child dysfunction and parental general health. Families caring for a child on HPN have normal healthy functioning.

Members of the family are affected by a child's medical condition and, in turn, the way in which the family adapts and copes will affect the course of some illnesses. Home management certainly reduces pressure on expensive hospital beds, but ultimately places more pressure on parents and the family.

The medical treatment of intestinal failure gives the chronically ill reason to hope, even if it produces limitations with which these persons have to live by making adjustments to meet everyday requirements. Our studies indicate that the loss of intestinal function does have a negative impact on aspects of QoL but this generates the question; is it the loss of intestinal function of the institution or nutritional support which causes this reduction? Intravenous nutrition is certainly not normal, but yet in some way it is reminiscent how each of us were all fed during the first 9 months of our existence.

References

Reference List

(1) Macht M, Meininger J, Roth J. The Pleasures of Eating: A Qualitive Analysis. Journal of Happiness Studies 2005; 6:137-160.

(2) Dudrick SJ. A clinical review of nutritional support of the patient. Am J Clin Nutr 1981; 34(6 Suppl):1191-1198.

(3) Fleming CR, Remington M. Intestinal Failure. In: Hill GR, editor. Nutrition and the Surgical Patient. New York: Churchill Livingstone, 1981: 219-235.

(4) Candusso M, Faraguna D, Sperli D, Dodaro N. Outcome and quality of life in paediatric home parenteral nutrition. Curr Opin Clin Nutr Metab Care 2002; 5(3):309-314.

(5) Gupte GL, Beath SV, Kelly DA, Millar AJ, Booth IW. Current issues in the management of intestinal failure. Arch Dis Child 2006; 91(3):259-264.

(6) O'Keefe SJ, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin Gastroenterol Hepatol 2006; 4(1):6-10.

(7) Shaffer J. Definition and service development. Clinical Nutrition 2002; 21(Supplement 1):144-145.

(8) A Strategic Framework for Intestinal Failure and Home Parenteral Nutrition Services for Adults in England. http://www.specialisedcommissioning.nhs.uk/index.php/key-documents/intestinal-failure-and-home-parenteral-nutrition/. 2008.

(9) Ney D. Insulin-Like Growth Factors in Relation to Gastrointestinal Diseases and Parenteral Nutrition. In: Houston SM, Holly JMP, Feldman EL, editors. IGF and Nutrition in Health and Disease. New Jersey: Humana Press Inc., 2005: 271-290.

(10) Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology 2003; 124(4):1111-1134.

(11) Irving M. Intestinal failure. J Gastroenterol Hepatol 2000; 15 Suppl:G26-G29.

(12) Jeejeebhoy KN, Langer B. Home parenteral nutrition. Can Med Assoc J 1980; 122(2):143-144.

(13) Johnston JE. Home parenteral nutrition: the "costs" of patient and family participation. Soc Work Health Care 1981; 7(2):49-66.

(14) Puntis JWL. Paediatric parenteral nutrition. In: Payne-James J, Grimble GK, Silk DBA, editors. Artificial Nutritional Support in Clinical Practice. London: Greenwich Medical Media Ltd., 2002: 461-484.

(15) Harries JT. Intravenous feeding in infants. Arch Dis Child 1971; 46(250):855-863.

(16) Knafelz D, Gambarara M, Diamanti A, Papadatou B, Ferretti F, Tarissi DI, I et al. Complications of home parenteral nutrition in a large pediatric series. Transplant Proc 2003; 35(8):3050-3051.

(17) Allen S, Lagunju I. The management of severe malnutrition: taking a broader view. Arch Dis Child 2007; 92(3):191-192.

(18) Scholl TO, Johnston FE, Cravioto J, DeLicardie ER, Lurie DS. The relationship of growth failure (chronic undernutrition) to the prevalence of clinically severe protein-energy malnutrition and to growth retardation in protein-energy malnutrition. Am J Clin Nutr 1979; 32(4):872-878.

(19) Chilton M, Chyatte M, Breaux J. The negative effects of poverty & food insecurity on child development. Indian J Med Res 2007; 126(4):262-272.

(20) Karlberg J, Engstrom I, Karlberg P, Fryer JG. Analysis of linear growth using a mathematical model. I. From birth to three years. Acta Paediatr Scand 1987; 76(3):478-488.

(21) Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976; 51(3):170-179.

(22) Gokhale R, Kirschner BS. Transition of care between paediatric and adult gastroenterology. Assessment of growth and nutrition. Best Pract Res Clin Gastroenterol 2003; 17(2):153-162.

(23) Heird WC, Winters RW. Total parenteral nutrition. The state of the art. J Pediatr 1975; 86(1):2-16.

(24) Wainwright PE, Colombo J. Nutrition and the development of cognitive functions: interpretation of behavioral studies in animals and human infants. Am J Clin Nutr 2006; 84(5):961-970.

(25) Shonkoff JP. From neurons to neighborhoods: old and new challenges for developmental and behavioral pediatrics. J Dev Behav Pediatr 2003; 24(1):70-76.

(26) Grantham-McGregor SM, Walker SP, Chang S. Nutritional deficiencies and later behavioural development. Proc Nutr Soc 2000; 59(1):47-54.

(27) Grantham-McGregor S. A review of studies of the effect of severe malnutrition on mental development. J Nutr 1995; 125(8 Suppl):2233S-2238S.

(28) Galler JR, Ramsey F, Solimano G, Kucharski LT, Harrison R. The influence of early malnutrition on subsequent behavioral development. IV. Soft neurologic signs. Pediatr Res 1984; 18(9):826-832.

(29) Grantham-McGregor S. Linear growth retardation and cognition. Lancet 2002; 359(9306):542.

(30) Gardner JM, Grantham-McGregor SM. Physical activity, undernutrition and child development. Proc Nutr Soc 1994; 53(1):241-248.

(31) Vargas JH, Ament ME, Berquist WE. Long-term home parenteral nutrition in pediatrics: ten years of experience in 102 patients. J Pediatr Gastroenterol Nutr 1987; 6(1):24-32.

(32) Goulet OJ, Revillon Y, Jan D, de Potter S, Maurage C, Lortat-Jacob S et al. Neonatal short bowel syndrome. J Pediatr 1991; 119(1 (Pt 1)):18-23.

(33) Booth IW, Lander AD. Short bowel syndrome. Baillieres Clin Gastroenterol 1998; 12(4):739-773.

(34) Robb RA, Brakebill JI, Ivey MF, Christensen DB, Young JH, Scribner BH. Subjective assessment of patient outcomes of home parenteral nutrition. Am J Hosp Pharm 1983; 40(10):1646-1650.

(35) Ricour C, Duhamel JF, Arnaud-Battandier F, Collard Y, Revillon Y, Nihoul-Fekete C. Enteral and parenteral nutrition in the short bowel syndrome in children. World J Surg 1985; 9(2):310-315.

(36) Fleming CR, McGill DB, Berkner S. Home parenteral nutrition as primary therapy in patients with extensive Crohn's disease of the small bowel and malnutrition. Gastroenterology 1977; 73(5):1077-1081.

(37) Dickerson RN, Brown RO. Parenteral and enteral nutrition in the home and chronic care settings. Am J Manag Care 1998; 4(3):445-455.

(38) Huisman-de Waal G, Naber T, Schoonhoven L, Persoon A, Sauerwein H, van Achterberg T. Problems experienced by patients receiving parenteral nutrition at home: results of an open interview study. JPEN J Parenter Enteral Nutr 2006; 30(3):215-221.

(39) Burnham WR. Nutritional support of patients with gastrointestinal disease. Br J Clin Pharmacol 1982; 14(3):315-324.

(40) Woodcock NP, Zeigler D, Palmer MD, Buckley P, Mitchell CJ, MacFie J. Enteral versus parenteral nutrition: a pragmatic study. Nutrition 2001; 17(1):1-12.

(41) Shils ME. Recalling a 63-year nutrition odyssey. Nutrition 2000; 16(7-8):582-585.

(42) American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. Gastroenterology 2003; 124(4):1105-1110.

(43) Goulet O, Ruemmele F, Lacaille F, Colomb V. Irreversible intestinal failure. J Pediatr Gastroenterol Nutr 2004; 38(3):250-269.

(44) Pironi L, Forbes A, Joly F, Colomb V, Lyszkowska M, Van Gossum A et al. Survival of patients identified as candidates for intestinal transplantation: a 3-year prospective follow-up. Gastroenterology 2008; 135(1):61-71.

(45) Read NW. Role of gastrointestinal factors in hunger and satiety in man. Proc Nutr Soc 1992; 51(1):7-11.

(46) Read N, French S, Cunningham K. The role of the gut in regulating food intake in man. Nutr Rev 1994; 52(1):1-10.

(47) Murray CD, le Roux CW, Gouveia C, Bassett P, Ghatei MA, Bloom SR et al. The effect of different macronutrient infusions on appetite, ghrelin and peptide YY in parenterally fed patients. Clin Nutr 2006; 25(4):626-633.

(48) Giduck SA, Threatte RM, Kare MR. Cephalic reflexes: their role in digestion and possible roles in absorption and metabolism. J Nutr 1987; 117(7):1191-1196.

(49) Gil KM, Skeie B, Kvetan V, Friedman MI, Askanazi J. Parenteral nutrition and oral intake: effect of branched-chain amino acids. Nutrition 1990; 6(4):291-295.

(50) Gil KM, Skeie B, Kvetan V, Askanazi J, Friedman MI. Parenteral nutrition and oral intake: effect of glucose and fat infusions. JPEN J Parenter Enteral Nutr 1991; 15(4):426-432.

(51) Jordan HA, Moses H, III, MacFayden BV, Jr., Dudrick SJ. Hunger and satiety in humans during parenteral hyperalimentation. Psychosom Med 1974; 36(2):144-155.

(52) McCutcheon NB, Tennissen AM. Hunger and appetitive factors during total parenteral nutrition. Appetite 1989; 13(2):129-141.

(53) Stratton RJ, Elia M. The effects of enteral tube feeding and parenteral nutrition on appetite sensations and food intake in health and disease. Clin Nutr 1999; 18(2):63-70.

(54) Woods SC. Gastrointestinal satiety signals I. An overview of gastrointestinal signals that influence food intake. Am J Physiol Gastrointest Liver Physiol 2004; 286(1):G7-13.

(55) Phillips RJ, Powley TL. Gastric volume rather than nutrient content inhibits food intake. Am J Physiol 1996; 271(3 Pt 2):R766-R769.

(56) French SJ, Conlon CA, Mutuma ST, Arnold M, Read NW, Meijer G et al. The effects of intestinal infusion of long-chain fatty acids on food intake in humans. Gastroenterology 2000; 119(4):943-948.

(57) Powley TL, Phillips RJ. Gastric satiation is volumetric, intestinal satiation is nutritive. Physiol Behav 2004; 82(1):69-74.

(58) Stratton RJ. The impact of nutritional support on appetite and food intake. Clinical Nutrition 2001; 20(Supplement 1):147-152.

(59) Oz V, Theilla M, Singer P. Eating habits and quality of life of patients receiving home parenteral nutrition in Israel. Clin Nutr 2008; 27(1):95-99.

(60) Fleming CR, Beart RW, Jr., Berkner S, McGill DB, Gaffron R. Home parenteral nutrition for management of the severely malnourished adult patient. Gastroenterology 1980; 79(1):11-18.

(61) Messing B, Landais P, Goldfarb B, Irving M. Home Parenteral Nutrition in adults: a multicentre survey in Europe. Clin Nutr 1989; 8(1):3-9.

(62) Messing B, Bories C, Kunstlinger F, Bernier JJ. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? Gastroenterology 1983; 84(5 Pt 1):1012-1019.

(63) Dowling RH. Small bowel adaptation and its regulation. Scand J Gastroenterol Suppl 1982; 74:53-74.

(64) Thiesen A, Drozdowski L, Iordache C, Neo CC, Woudstra TD, Xenodemetropoulos T et al. Adaptation following intestinal resection: mechanisms and signals. Best Pract Res Clin Gastroenterol 2003; 17(6):981-995.

(65) Howard L, Hassan N. Home parenteral nutrition. 25 years later. Gastroenterol Clin North Am 1998; 27(2):481-512.

(66) PULLAN JM. Massive intestinal resection. Proc R Soc Med 1959; 52(1):31-37.

(67) Weinstein LD, Shoemaker CP, Hersh T, Wright HK. Enhanced intestinal absorption after small bowel resection in man. Arch Surg 1969; 99(5):560-562.

(68) Solhaug JH, Tvete S. Adaptative changes in the small intestine following bypass operation for obesity. A radioglocal and histological study. Scand J Gastroenterol 1978; 13(4):401-408.

(69) Doldi SB. Intestinal adaptation following jejuno-ileal bypass. Clin Nutr 1991; 10(3):138-145.

(70) Dowling RH, Booth CC. Functional compensation after small-bowel resection in man. Demonstration by direct measurement. Lancet 1966; 2(7455):146-147.

(71) Bryant J. Observations upon the growth and length of the human intestine. American Journal of the Medical Sciences 1924; 167:499-520.

(72) Dudrick SJ, Latifi R, Fosnocht DE. Management of the short-bowel syndrome. Surg Clin North Am 1991; 71(3):625-643.

(73) Carbonnel F, Cosnes J, Chevret S, Beaugerie L, Ngo Y, Malafosse M et al. The role of anatomic factors in nutritional autonomy after extensive small bowel resection. JPEN J Parenter Enteral Nutr 1996; 20(4):275-280.

(74) Welters CF, Dejong CH, Deutz NE, Heineman E. Intestinal adaptation in short bowel syndrome. ANZ J Surg 2002; 72(3):229-236.

(75) Nightingale JM, Lennard-Jones JE, Walker ER, Farthing MJ. Jejunal efflux in short bowel syndrome. Lancet 1990; 336(8718):765-768.

(76) Lloyd DA, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence on home parenteral nutrition: experience over a 25-year period in a UK referral centre. Aliment Pharmacol Ther 2006; 24(8):1231-1240.

(77) Ingham Clark CL, Lear PA, Wood S, Lennard-Jones JE, Wood RF. Potential candidates for small bowel transplantation. Br J Surg 1992; 79(7):676-679.

(78) Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology 1999; 117(5):1043-1050.

(79) de Francesco A, Bertinet DB, Fadda M, Gallenca P, Malfi G, Palmo A. Long-term parenteral nutrition in adults: outcomes and quality of life. Clinical Nutrition 2001; 20:3-5.

(80) Weale AR, Edwards AG, Bailey M, Lear PA. Intestinal adaptation after massive intestinal resection. Postgrad Med J 2005; 81(953):178-184.

(81) Kurkchubasche AG, Rowe MI, Smith SD. Adaptation in short-bowel syndrome: reassessing old limits. J Pediatr Surg 1993; 28(8):1069-1071.

(82) Puntis JW. Nutritional support at home and in the community. Arch Dis Child 2001; 84(4):295-298.

(83) Weber TR, Tracy T, Jr., Connors RH. Short-bowel syndrome in children. Quality of life in an era of improved survival. Arch Surg 1991; 126(7):841-846.

(84) Levy E, Frileux P, Sandrucci S, Ollivier JM, Masini JP, Cosnes J et al. Continuous enteral nutrition during the early adaptive stage of the short bowel syndrome. Br J Surg 1988; 75(6):549-553.

(85) Rossi L, Kadamba P, Hugosson C, De Vol EB, Habib Z, Al Nassar S. Pediatric short bowel syndrome: adaptation after massive small bowel resection. J Pediatr Gastroenterol Nutr 2007; 45(2):213-221.

(86) Dorney SF, Ament ME, Berquist WE, Vargas JH, Hassall E. Improved survival in very short small bowel of infancy with use of long-term parenteral nutrition. J Pediatr 1985; 107(4):521-525.

(87) Dudley HA, SINCLAIR IS, McLAREN IF, McNAIR TJ, NEWSAM JE. Intestinal pseudo-obstruction. J R Coll Surg Edinb 1958; 3(3):206-217.

(88) Steigmann FD, Singer HA. Idiopathic spastic ileus with fatal termination. The American Journal of Surgery 1935; 27(2):342-348.

(89) Christensen J, Dent J, Malagelada JR, Wingate DL. Pseudo-obstruction. Gastroenterology International 1990; 3:107-119.

(90) Schwankovsky L, Mousa H, Rowhani A, Di Lorenzo C, Hyman PE. Quality of life outcomes in congenital chronic intestinal pseudo-obstruction. Dig Dis Sci 2002; 47(9):1965-1968.

(91) Kamm MA. Intestinal pseudo-obstruction. Gut 2000; 47 Suppl 4:iv84.

(92) Stanghellini V, Corinaldesi R, Barbara L. Pseudo-obstruction syndromes. Baillieres Clin Gastroenterol 1988; 2(1):225-254.

(93) Powell-Tuck J, Martin J, Domizio P, Wingate D. Intestinal Pseudo-obstruction. In: Nightingale JM, editor. Intestinal Failure. London: Greenwich Medical Media Limited, 2001: 125-139.

(94) Wingate D, Hongo M, Kellow J, Lindberg G, Smout A. Disorders of gastrointestinal motility: towards a new classification. J Gastroenterol Hepatol 2002; 17 Suppl:S1-14.

(95) Hirano I, Pandolfino J. Chronic intestinal pseudo-obstruction. Dig Dis 2000; 18(2):83-92.

(96) Annan G. An exhibition of books on the growth of our knowledge of blood transfusion. Bull NY Acad Med 1939; 15:622.

(97) Jardine L. On a Grander Scale. The outstanding life and tumultuous times of Sir Christopher Wren. New York: Harper Collins, 2002.

(98) Major R. A History of Medicine. Springfield Illinois: Charles C Thomas, 1954.

(99) Geyer R. Parenteral Nutrition. Physiol Rev 1960; 40:150.

(100) Annan G. Blood Transfusion in the Nineteenth Century. Bull NY Acad Med 1939; 15:626.

(101) Latta T. Injections of saline solutions in extraordinary quantities into the veins in cases of malignant cholera. Lancet 1832; 2:243.

(102) Dudrick SJ, Rhoads JE. New horizons for intravenous feeding. JAMA 1971; 215(6):939-949.

(103) Hodder E. Transfer of Milk in Cholera. Practitioner 1873; 10:14.

(104) Law DH. Total parenteral nutrition. Adv Intern Med 1972; 18:389-410.

(105) Karran S, Alberti K. Practical Nutritional Support. UK: Pitman Medical Publishing co. Ltd , 1980.

(106) Seibert F. Fever Producing Substance Found in Some Distilled Waters. Am J physiol 1923; 67(90).

(107) Phillips D, Odgers O. Background and perspectives. Parenteral and Enteral Nutrition: a practical guide. GB: Churchill Livingstone, 1986: 1-6.

(108) Elman R, Weiner DO. Intravenous alimentation with special reference to protein (amino acid) metabolism. JAMA 1939; 112:796-802.

(109) Helfrick FW, Abelson NM. Intravenous feeding of a complete diet in a child: Report of a case. J Pediatr 1944; 25(5):400-403.

(110) Helfrick FW, Abelson NM. Intravenous feeding of a complete diet in a child: report of a case. JPEN J Parenter Enteral Nutr 1978; 2(5):688-689.

(111) Aubaniac R. L'injection intraveineuse sous-claviculaire: advantages et technique. Med 1952; 60:1456.

(112) MENG HC, Early F. Study of complete parenteral alimentation on dogs. J Lab Clin Med 1949; 34(8):1121-1132.

(113) LEVINE RS, CALVARY EC, PLZAK JE, ALLEN JG. Effect of parenterally administered fat emulsion on nitrogen retention: attempts at complete parenteral alimentation in dogs. Metabolism 1957; 6(6 Pt 2):597-606.

(114) Hakansson I, Holm I, Wretlind A. Studies of complete intravenous alimentation in dogs. Nutr Dieta Eur Rev Nutr Diet 1966; 8(1):1-21.

(115) Dudrick S, Vars H, Rhoads J. Growth of puppies receiving all nutritional requirements by vein. Fortschritte der parenteralen Ernahrung 1967; International Society of Parenteral Nutrition Munich:2.

(116) Copeland EM, III. Heroes and friends. Ann Surg 2000; 231(5):617-623.

(117) Dudrick SJ. Intravenous feeding as an aid to nutrition in disease. CA Cancer J Clin 1970; 20(4):198-211.

(118) Edgren B, Wretlind A. The theoretical background of the intravenous nutrition with fat emulsions. Nutr Diet 1963; 5:364.

(119) Beal JM, Payne MA, Gilder H, Johnson GJr, Craver W. Experience with administration of an intravenous fat emulsion to surgical pateints. Metabolism 1957; 6:673-681.

(120) Dudrick S, Wilmore D, Vars H, Rhoads J. Nutrition classics. Surgery, Volume 64, 1968. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Nutr Rev 1981; 39(7):278-281.

(121) Holden WD, Kreiger H, Levey S, Abbott WE. The effect of nutrition on nitrogen metabolism in the surgical patient. Ann Surg 1957; 146:563.

(122) Rhoads JE. The development of TPN: an interview with pioneer surgical nutritionist Jonathan E. Rhoads, MD. [Interview by Carolyn T. Spencer and Charlene Compher]. J Am Diet Assoc 2001; 101(7):747-750.

(123) Fischer JE. Hyperalimentation. Adv Surg 1977; 11:1-69.

(124) Medical staff conference. Total parenteral nutrition--state of the art. West J Med 1977; 127(5):397-403.

(125) Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. JAMA 1968; 203(10):860-864.

(126) Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Can intravenous feeding as the sole means of nutrition support growth in the child and restore weight loss in an adult? An affirmative answer. Ann Surg 1969; 169(6):974-984.

(127) Filler RM, Eraklis AJ, Rubin VG, Das JB. Long-term total parenteral nutrition in infants. N Engl J Med 1969; 281(11):589-594.

(128) Layden T, Rosenberg F, Nemchausky G, Elson C, Rosenberg I. Reversal of growth arrest in adolescents with Crohn's disease after parenteral alimentation. Gastroenterology 1976; 70(6):1017-1021.

(129) Strobel CT, Byrne WJ, Ament ME. Home parenteral nutrition in children with Crohn's disease: an effective management alternative. Gastroenterology 1979; 77(2):272-279.

(130) Kirschner BS, Klich JR, Kalman SS, deFavaro MV, Rosenberg IH. Reversal of growth retardation in Crohn's disease with therapy emphasizing oral nutritional restitution. Gastroenterology 1981; 80(1):10-15.

(131) Peden VH, Karpel JT. Total parenteral nutrition in premature infants. J Pediatr 1972; 81(1):137-144.

(132) Johnson JD, Albritton WL, Sunshine P. Hyperammonemia accompanying parenteral nutrition in newborn infants. J Pediatr 1972; 81(1):154-161.

(133) Irving M. Intravenous nutrition: the materials available. Proc R Soc Med 1973; 66(8):767-770.

(134) Thompson SW. The Pathology of Parenteral Nutrition with Lipids. In: Thomas CC, editor. Springfield Ill.: 2004.

(135) LEVEEN HH, GIORDANO P, SPLETZER J. Mechanism of removal of intravenously injected fat. Its relationship to toxioity. Arch Surg 1961; 83:311-321.

(136) Wretlind A. The Phamacological Basis For The Use of Fat Emulsions in Intavenous Nutrition. Acta Chir Scand 1964; 86:SUPPL.

(137) Heird WC, Driscoll JM, Jr. Use of intravenously administered lipid in neonates. Pediatrics 1975; 56(1):5-7.

(138) Eckart J, Adolph M, van der MU, Naab V. Fat emulsions containing medium chain triglycerides in parenteral nutrition of intensive care patients. JPEN J Parenter Enteral Nutr 1980; 4(4):360-366.

(139) Guisard D, Debry G. Metabolic effects of a medium-chain triglyceride emulsion injected intravenously in man. Horm Metab Res 1972; 4(6):509.

(140) Wahed M, Geoghegan M, Powell-Tuck J. Novel substrates. Eur J Gastroenterol Hepatol 2007; 19(5):365-370.

(141) De Nardi L, Bellinati-Pires R, Torrinhas RS, Bacchi CE, Arias V, Waitzberg DL. Effect of fish oil containing parenteral lipid emulsions on neutrophil chemotaxis and resident-macrophages' phagocytosis in rats. Clin Nutr 2008; 27(2):283-288.

(142) Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. Am J Clin Nutr 2007; 85(5):1171-1184.

(143) Schlotzer E, Kanning U. Elimination and tolerance of a new parenteral lipid emulsion (SMOF)--a double-blind cross-over study in healthy male volunteers. Ann Nutr Metab 2004; 48(4):263-268.

(144) Jeejeebhoy KN, Anderson GH, Nakhooda AF, Greenberg GR, Sanderson I, Marliss EB. Metabolic studies in total parenteral nutrition with lipid in man. Comparison with glucose. J Clin Invest 1976; 57(1):125-136.

(145) Pithie AD, Pennington CR. The incidence aetiology and management of central vein thrombosis during parenteral nutrition. Clin Nutr 1987; 6:151-153.

(146) Johnston DA, Pennington CR. Home parenteral nutrition in Tayside 1980-1992. Scott Med J 1993; 38(4):110-111.

(147) Buchman AL, Ament ME, Sohel M, Dubin M, Jenden DJ, Roch M et al. Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: proof of a human choline requirement: a placebo-controlled trial. JPEN J Parenter Enteral Nutr 2001; 25(5):260-268.

(148) Dudrick SJ, Ruberg RL. Principles and practice of parenteral nutrition. Gastroenterology 1971; 61(6):901-910.

(149) Heird WC, Winters RW. Total intravenous alimentation in pediatric patients. South Med J 1975; 68(9):1173-1176.

(150) Hardy G. Pharmaceutical aspects of parenteral nutrition: a historical perspective. Nutrition 1995; 11(6):767-768.

(151) Hardy G. Contributions of industry to parenteral nutrition. Clin Nutr 2003; 22 Suppl 2:S73-S76.

(152) Solassol C, Joyeux H, Etco L, Pujol H, Romieu C. New techniques for long-term intravenous feeding: an artificial gut in 75 patients. Ann Surg 1974; 179(4):519-522.

(153) Powell-Tuck J, Nielsen T, Farwell JA, Lennard-Jones JE. Team approach to long-term intravenous feeding in patients with gastrointestinal disorders. Lancet 1978; 2(8094):825-828.

(154) Kirschner BS, Voinchet O, Rosenberg IH. Growth retardation in inflammatory bowel disease. Gastroenterology 1978; 75(3):504-511.

(155) Owings JM, Bomar WE, Jr., Ramage RC. Parenteral hyperalimentation and its practical applications. Ann Surg 1972; 175(5):712-719.

(156) Dudrick SJ, O'Donnell JJ, Englert DM, Matheny RG, Blume ER, Nutt RE et al. 100 patient-years of ambulatory home total parenteral nutrition. Ann Surg 1984; 199(6):770-781.

(157) Machleder HI. Intravenous Hyperalimentation. Calif Med 1971; 114(3):66-67.

(158) Scribner BH, Cole JJ, Christopher TG, Vizzo JE, Atkins RC, Blagg CR. Long-term total parenteral nutrition. The concept of an artificial gut. JAMA 1970; 212(3):457-463.

(159) Broviac JW, Scribner BH. Prolonged parenteral nutrition in the home. Surg Gynecol Obstet 1974; 139(1):24-28.

(160) Heizer WD, Orringer EP. Parenteral nutrition at home for 5 years via arteriovenous fistulae. Supplemental intravenous feedings for a patient with severe short bowel syndrome. Gastroenterology 1977; 72(3):527-532.

(161) Jeejeebhoy KN, Zohrab WJ, Langer B, Phillips MJ, Kuksis A, Anderson GH. Total parenteral nutrition at home for 23 months, without complication, and with good rehabilitation. A study of technical and metabolic features. Gastroenterology 1973; 65(5):811-820.

(162) Jeejeebhoy KN, Langer B, Tsallas G, Chu RC, Kuksis A, Anderson GH. Total parenteral nutrition at home: studies in patients surviving 4 months to 5 years. Gastroenterology 1976; 71(6):943-953.

(163) Shils ME, Wright WL, Turnbull A, Brescia F. Long-term parenteral nutrition through an external arteriovenous shunt. N Engl J Med 1970; 283(7):341-344.

(164) Scribner BH, Riella M. The Artificial Gut System (AGS) for Home Parenteral Nutrition. Gastroenterology 1975; 68(4):983.

(165) Byrne WJ, Halpin TC, Asch MJ, Fonkalsrud EW, Ament ME. Home total parenteral nutrition: an alternative approach to the management of children with severe chronic small bowel disease. J Pediatr Surg 1977; 12(3):359-366.

(166) Scribner BH, Cole JJ. Evolution of the technique of home parenteral nutrition. JPEN J Parenter Enteral Nutr 1979; 3(2):58-61.

(167) Broviac JW, Cole JJ, Scribner BH. A silicone rubber atrial catheter for prolonged parenteral alimentation. Surg Gynecol Obstet 1973; 136(4):602-606.

(168) Riella MC, Scribner BH. Five years' experience with a right atrial catheter for prolonged parenteral nutrition at home. Surg Gynecol Obstet 1976; 143(2):205-208.

(169) Ward MW, Harrison RA, Doyle J, Clark CG. Parenteral nutrition at home. Practitioner 1984; 228(1395):831-833.

(170) Richards DM, Deeks JJ, Sheldon TA, Shaffer JL. Home parenteral nutrition: a systematic review. Health Technol Assess 1997; 1(1):i-59.

(171) Shils ME. A program for total parenteral nutrition at home. Am J Clin Nutr 1975; 28(12):1429-1435.

(172) Bordos DC, Cameron JL. Successful long-term intravenous hyperalimentation in the hospital and at home. Arch Surg 1975; 110(4):439-441.

(173) Ivey M, Riella M, Mueller W, Scribner B. Long-term parenteral nutrition in the home. Am J Hosp Pharm 1975; 32(10):1032-1036.

(174) Wolfe BM, Beer WH, Hayashi JT, Halsted CH, Cannon RA, Cox KL. Experience with home parenteral nutrition. Am J Surg 1983; 146(1):7-14.

(175) Jones BJ. Recent developments in the delivery of home parenteral nutrition in the UK. Proc Nutr Soc 2003; 62(3):719-725.

(176) Howard L, Ament M, Fleming CR, Shike M, Steiger E. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. Gastroenterology 1995; 109(2):355-365.

(177) Strobel CT, Byrne WJ, Fonkalsrud EW, Ament ME. Home parenteral nutrition: results in 34 pediatric patients. Ann Surg 1978; 188(3):394-403.

(178) Goldberger JH, DeLuca FG, Wesselhoeft CW, Randall HT. A home program of long-term total parenteral nutrition in children. J Pediatr 1979; 94(2):325-328.

(179) Byrne WJ, Ament ME, Burke M, Fonkalsrud E. Home parenteral nutrition. Surg Gynecol Obstet 1979; 149(4):593-599.

(180) Cannon RA, Byrne WJ, Ament ME, Gates B, O'Connor M, Fonkalsrud EW. Home parenteral nutrition in infants. J Pediatr 1980; 96(6):1098-1104.

(181) Manual of Dietetic Practice. 4th ed. Oxford: Blackwell Science, 2007.

(182) Colomb V, Goulet O, Ricour C. Home enteral and parenteral nutrition in children. Baillieres Clin Gastroenterol 1998; 12(4):877-894.

(183) Ksiazyk J, Lyszkowska M, Kierkus J, Bogucki K, Ratynska A, Tondys B et al. Home parenteral nutrition in children: the Polish experience. J Pediatr Gastroenterol Nutr 1999; 28(2):152-156.

(184) Contemporary Nutrition Support Practice. A Clinical Guide. 2nd ed. Missouri: Saunders, 2003.

(185) Lerebours E, Rimbert A, Hecketsweiler B, Hellot MF, Denis P, Colin R. Comparison of the effects of continuous and cyclic nocturnal parenteral

nutrition on energy expenditure and protein metabolism. JPEN J Parenter Enteral Nutr 1988; 12(4):360-364.

(186) Maini B, Blackburn GL, Bistrian BR, Flatt JP, Page JG, Bothe A et al. Cyclic hyperalimentation: an optimal technique for preservation of visceral protein. J Surg Res 1976; 20(6):515-525.

(187) Just B, Messing B, Darmaun D, Rongier M, Camillo E. Comparison of substrate utilization by indirect calorimetry during cyclic and continuous total parenteral nutrition. Am J Clin Nutr 1990; 51(1):107-111.

(188) Sanderson I, Deitel M. Intravenous hyperalimentation without sepsis. Surg Gynecol Obstet 1973; 136(4):577-585.

(189) Lloyd DA, Gabe SM. Managing liver dysfunction in parenteral nutrition. Proc Nutr Soc 2007; 66(4):530-538.

(190) Lloyd DA, Zabron AA, Gabe SM. Chronic biochemical cholestasis in patients receiving home parenteral nutrition: prevalence and predisposing factors. Aliment Pharmacol Ther 2008; 27(7):552-560.

(191) Williams N, Wales S, Bradley A, Barber D, Shaffer J, Irving M. Long-term glucose homeostasis in patients on home parenteral nutrition. Clin Nutr 1996; 15(3):141-142.

(192) Sanderson I, Deitel M. Insulin response in patients receiving concentrated infusions of glucose and casein hydrolysate for complete parenteral nutrition. Ann Surg 1974; 179(4):387-394.

(193) Hardy G. Manganese in parenteral nutrition: who, when, and why should we supplement? Gastroenterology 2009; 137(5 Suppl):S29-S35.

(194) Elia M, Stratton RJ, Holden C, Meadows N, Micklewright A, Russell C et al. Home artificial nutritional support: the value of the British Artificial Nutrition Survey. Clinical Nutrition 2001; 20:61-66.

(195) Powell-Tuck J. Central venous feeding. J R Soc Med 1979; 72(11):798-800.

(196) Schmidt-Sommerfeld E, Snyder G, Rossi TM, Lebenthal E. Catheter-related complications in 35 children and adolescents with gastrointestinal disease on home parenteral nutrition. JPEN J Parenter Enteral Nutr 1990; 14(2):148-151.

(197) Silver HJ, Wellman NS, Galindo-Ciocon D, Johnson P. Family caregivers of older adults on home enteral nutrition have multiple unmet task-related training needs and low overall preparedness for caregiving. J Am Diet Assoc 2004; 104(1):43-50.

(198) Lehoux P, Saint-Arnaud J, Richard L. The use of technology at home: what patient manuals say and sell vs. what patients face and fear. Sociol Health Illn 2004; 26(5):617-644.

(199) Bisset WM, Stapleford P, Long S, Chamberlain A, Sokel B, Milla PJ. Home parenteral nutrition in chronic intestinal failure. Arch Dis Child 1992; 67(1):109-114.

(200) Ricour C, Gorski AM, Goulet O, de Potter S, Corriol O, Postaire M et al. Home parenteral nutrition in children: 8 years of experience with 112 patients. Clin Nutr 1990; 9(2):65-71.

(201) Gambarara M, Ferretti F, Papadatou B, Diamanti A, Castro M. Central vein catheter-related complications associated with home parenteral nutrition in children: experience in 41 patients. Nutrition 2001; 17(11-12):970-971.

(202) Holden C. Review of home paediatric parenteral nutrition on the UK. Br J Nurs 2001; 10(12):782-788.

(203) Meadows N. Home Parenteral Nutrition in Children. Bailliere's Clinical Paediatrics 1997; 5(2):189-198.

(204) Berry RK, Jorgensen S. Growing with home parenteral nutrition: adjusting to family life and child development (Part 1 of a two-part series). Pediatr Nurs 1988; 14(1):43-45.

(205) Engstrom I, Bjornestam B, Finkel Y. Psychological distress associated with home parenteral nutrition in Swedish children, adolescents, and their parents: preliminary results. J Pediatr Gastroenterol Nutr 2003; 37(3):246-250.

(206) Henwood M. Ignored and Invisible: report of a UK research survey commissioned by Carers National Association. London: 1998.

(207) Leonard BJ, Brust JD, Nelson RP. Parental distress: caring for medically fragile children at home. J Pediatr Nurs 1993; 8(1):22-30.

(208) Lehoux P. Patients' perspectives on high-tech home care: a qualitative inquiry into the user-friendliness of four technologies. BMC Health Serv Res 2004; 4(1):28.

(209) Buchman AL. Complications of long-term home total parenteral nutrition: their identification, prevention and treatment. Dig Dis Sci 2001; 46(1):1-18.

(210) Herfindal ET, Bernstein LR, Kudzia K, Wong A. Survey of home nutritional support patients. JPEN J Parenter Enteral Nutr 1989; 13(3):255-261.

(211) Keighley BD, MacGregor AR. Total parenteral nutrition at home: the implications for a rural practice. J R Coll Gen Pract 1980; 30(215):354-357.

(212) Smith CE. A model of caregiving effectiveness for technologically dependent adults residing at home. ANS Adv Nurs Sci 1994; 17(2):27-40.

(213) Arzouman JM, Dudas S, Ferrans CE, Holm K. Quality of life of patients with sarcoma postchemotherapy. Oncol Nurs Forum 1991; 18(5):889-894.

(214) Landgraf JM, Maunsell E, Speechley KN, Bullinger M, Campbell S, Abetz L et al. Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results. Qual Life Res 1998; 7(5):433-445.

(215) Thorne SE, Radford MJ, Armstrong EA. Long-term gastrostomy in children: caregiver coping. Gastroenterol Nurs 1997; 20(2):46-53.

(216) Berry RK, Jorgensen S. Growing with home parenteral nutrition: maintaining a safe environment. (2). Pediatr Nurs 1988; 14(2):155-157.

(217) Johnson T, Sexton E. Managing children and adolescents on parenteral nutrition: Challenges for the nutritional support team. Proc Nutr Soc 2006; 65(3):217-221.

(218) Candusso M, Giglio L, Faraguna D. Long-term home parenteral nutrition in children. Clin Nutr 1995; 14 Suppl 1:28-32.

(219) Wong C, Akobeng AK, Miller V, Thomas AG. Quality of life of parents of children on home parenteral nutrition. Gut 2000; 46(2):294-295.

(220) Grootenhuis MA, Last BF. Adjustment and coping by parents of children with cancer: a review of the literature. Support Care Cancer 1997; 5(6):466-484.

(221) Brook G. Quality of life issues: parenteral nutrition to small bowel transplantation--a review. Nutrition 1998; 14(10):813-816.

(222) Schor EL. Family pediatrics: report of the Task Force on the Family. Pediatrics 2003; 111(6 Pt 2):1541-1571.

(223) Ralston CW, O'Connor MJ, Ament M, Berquist W, Parmelee AH, Jr. Somatic growth and developmental functioning in children receiving prolonged home total parenteral nutrition. J Pediatr 1984; 105(5):842-846.

(224) Colomb V, Fabeiro M, Dabbas M, Goulet O, Merckx J, Ricour C. Central venous catheter-related infections in children on long-term home parenteral nutrition: incidence and risk factors. Clin Nutr 2000; 19(5):355-359.

(225) O'Hanrahan T, Irving MH. The Role of HPN in the Management of Intestinal Failure. Report of 400 Cases. Clinical Nutrition 1992; 11:331-336.

(226) Colomb V. Home parenteral nutrition: the pediatric point of view. Nutrition 1999; 15(2):172-173.

(227) Diamanti A, Gambarara M, Knafelz D, Marcellini M, Boldrini R, Ferretti F et al. Prevalence of liver complications in pediatric patients on home parenteral nutrition: indications for intestinal or combined liver-intestinal transplantation. Transplant Proc 2003; 35(8):3047-3049.

(228) Wang KW, Barnard A. Technology-dependent children and their families: a review. J Adv Nurs 2004; 45(1):36-46.

(229) Thyen U, Kuhlthau K, Perrin JM. Employment, child care, and mental health of mothers caring for children assisted by technology. Pediatrics 1999; 103(6 Pt 1):1235-1242.

(230) Kazak AE, Nachman GS. Family research on childhood chronic illness: pediatric oncology as an example. Journal of Family Psychology 1991; 4:462-483.

(231) Gottrand F, Staszewski P, Colomb V, Loras-Duclaux I, Guimber D, Marinier E et al. Satisfaction in different life domains in children receiving home parenteral nutrition and their families. J Pediatr 2005; 146(6):793-797.

(232) Ling LJ, Hershenson MB, Young S, Traisman HS. Home parenteral nutrition in a child with Menetrier disease. Eur J Pediatr 1986; 144(5):505-507.

(233) Diehl SF, Moffitt KA, Wade SM. Focus group interview with parents of children with medically complex needs: an intimate look at their perceptions and feelings. Child Health Care 1991; 20(3):170-178.

(234) Petit de Mange EA. Pediatric considerations in homecare. Crit Care Nurs Clin North Am 1998; 10(3):339-346.

(235) Sloper P. Predictors of distress in parents of children with cancer: a prospective study. J Pediatr Psychol 2000; 25(2):79-91.

(236) Kupst MJ, Schulman JL. Long-term coping with pediatric leukemia: a six-year follow-up study. J Pediatr Psychol 1988; 13(1):7-22.

(237) Morrow GR, Carpenter PJ, Hoagland AC. The role of social support in parental adjustment to pediatric cancer. J Pediatr Psychol 1984; 9(3):317-329.

(238) Speechley KN, Noh S. Surviving childhood cancer, social support, and parents' psychological adjustment. J Pediatr Psychol 1992; 17(1):15-31.

(239) Hardy MS, Armstrong FD, Routh DK, Albrecht J, Davis J. Coping and communication among parents and children with human immunodeficiency virus and cancer. J Dev Behav Pediatr 1994; 15(3 Suppl):S49-S53.

(240) Twoy R, Connolly PM, Novak JM. Coping strategies used by parents of children with autism. J Am Acad Nurse Pract 2007; 19(5):251-260.

(241) Azar R, Solomon CR. Coping strategies of parents facing child diabetes mellitus. J Pediatr Nurs 2001; 16(6):418-428.

(242) Staab D, Wenninger K, Gebert N, Rupprath K, Bisson S, Trettin M et al. Quality of life in patients with cystic fibrosis and their parents: what is important besides disease severity? Thorax 1998; 53(9):727-731.

(243) Mughal M, Irving M. Home parenteral nutrition in the United Kingdom and Ireland. Lancet 1986; 2(8503):383-387.

(244) Howard L. A global perspective of home parenteral and enteral nutrition. Nutrition 2000; 16(7-8):625-628.

(245) Moreno JM, Shaffer J, Staun M, Hebuterne X, Bozzetti F, Pertkiewicz M et al. Survey on legislation and funding of home artificial nutrition in different European countries. Clin Nutr 2001; 20(2):117-123.

(246) Jones BJ, Holden C, Stratton R, Micklewright A, Dalzell M. Annual BANS Report 2007 - Artificial Nutrition Support in the UK 2000 - 2006; http://www.bapen.org.uk/pdfs/bans_reports/bans_report_07.pdf. 2007.

(247) Colomb V, Ricour C. Home parenteral nutrition in children. Clin Nutr 2003; 22 Suppl 2:57-59.

(248) Colomb V. Home artificial nutritional support in gastrointestinal disease. Curr Opin Clin Nutr Metab Care 1998; 1(5):395-399.

(249) Colomb V, Dabbas-Tyan M, Taupin P, Talbotec C, Revillon Y, Jan D et al. Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. J Pediatr Gastroenterol Nutr 2007; 44(3):347-353.

(250) Howard L, Heaphey L, Fleming CR, Lininger L, Steiger E. Four years of North American registry home parenteral nutrition outcome data and their implications for patient management. JPEN J Parenter Enteral Nutr 1991; 15(4):384-393.

(251) Howard L. Home parenteral nutrition: survival, cost, and quality of life. Gastroenterology 2006; 130(2 Suppl 1):S52-S59.

(252) Scolapio JS, Fleming CR, Kelly DG, Wick DM, Zinsmeister AR. Survival of home parenteral nutrition-treated patients: 20 years of experience at the Mayo Clinic. Mayo Clin Proc 1999; 74(3):217-222.

(253) Fallowfield L. Quality of life: a new perspective for cancer patients. Nat Rev Cancer 2002; 2(11):873-879.

(254) Bozzetti F. Home total parenteral nutrition in cancer patients. Clin Nutr 1995; 14 Suppl 1:36-40.

(255) Bozzetti F, Amadori D, Bruera E, Cozzaglio L, Corli O, Filiberti A et al. Guidelines on artificial nutrition versus hydration in terminal cancer patients. European Association for Palliative Care. Nutrition 1996; 12(3):163-167.

(256) Gambarara M, Ferretti F, Papadatou B, Gastelli-Gattinara G, Diamanti A, Rivosecchi M et al. Long-term parenteral nutrition and parenteral nutrition dependency in pediatric patients. Transplant Proc 1998; 30(6):2543-2544.

(257) King LA, Carson LF, Konstantinides N, House MS, Adcock LL, Prem KA et al. Outcome assessment of home parenteral nutrition in patients with gynecologic malignancies: what have we learned in a decade of experience? Gynecol Oncol 1993; 51(3):377-382.

(258) Copeland EM, III, Macfadyen BV, Jr., McGown C, Dudrick SJ. The use of hyperalimentation in patients with potential sepsis. Surg Gynecol Obstet 1974; 138(3):377-380.

(259) Daly JM, Copeland EM, Dudrick SJ. Effects of intravenous nutrition on tumor growth and host immunocompetence in malnourished animals. Surgery 1978; 84(5):655-658.

(260) Bouletreau P, Gerard M, Messing B, Chambrier C, Gelas P, Robert D et al. Home parenteral nutrition and AIDS. Clin Nutr 1995; 14(4):213-218.

(261) Van Gossum A, Bakker H, Bozzetti F, Staun M, Leon-Sanz M, Hebuterne X et al. Home parenteral nutrition in adult: a European multicentre survey in 1997 ESPEN-home artificial nutrition working group. Clin Nutr 1999; 18(3):135-140.

(262) Sayers GM, Lloyd DA, Gabe SM. Parenteral nutrition: ethical and legal considerations. Postgrad Med J 2006; 82(964):79-83.

(263) Violante G, Alfonsi L, Santarpia L, Cillis MC, Negro G, De Caprio C et al. Adult home parenteral nutrition: a clinical evaluation after a 3-year experience in a Southern European centre. Eur J Clin Nutr 2006; 60(1):58-61.

(264) Jonkers-Schuitema CF. HPN=Home palliative care? Clin Nutr 2004; 23(6):1253-1255.

(265) August DA, Thorn D, Fisher RL, Welchek CM. Home parenteral nutrition for patients with inoperable malignant bowel obstruction. JPEN J Parenter Enteral Nutr 1991; 15(3):323-327.

(266) Chapman C, Bosscher J, Remmenga S, Park R, Barnhill D. A technique for managing terminally ill ovarian carcinoma patients. Gynecol Oncol 1991; 41(1):88-91.

(267) Cozzaglio L, Balzola F, Cosentino F, DeCicco M, Fellagara P, Gaggiotti G et al. Outcome of cancer patients receiving home parenteral nutrition. Italian Society of Parenteral and Enteral Nutrition (S.I.N.P.E.). JPEN J Parenter Enteral Nutr 1997; 21(6):339-342.

(268) Whitworth MK, Whitfield A, Holm S, Shaffer J, Makin W, Jayson GC. Doctor, does this mean I'm going to starve to death? J Clin Oncol 2004; 22(1):199-201.

(269) Hoda D, Jatoi A, Burnes J, Loprinzi C, Kelly D. Should patients with advanced, incurable cancers ever be sent home with total parenteral nutrition? A single institution's 20-year experience. Cancer 2005; 103(4):863-868.

(270) Bozzetti F, Cozzaglio L, Biganzoli E, Chiavenna G, De Cicco M, Donati D et al. Quality of life and length of survival in advanced cancer patients on home parenteral nutrition. Clin Nutr 2002; 21(4):281-288.

(271) Bozzetti F. Home total parenteral nutrition in incurable cancer patients: a therapy, a basic humane care or something in between? Clin Nutr 2003; 22(2):109-111.

(272) Orrevall Y, Tishelman C, Herrington MK, Permert J. The path from oral nutrition to home parenteral nutrition: a qualitative interview study of the experiences of advanced cancer patients and their families. Clin Nutr 2004; 23(6):1280-1287.

(273) Orrevall Y, Tishelman C, Permert J. Home parenteral nutrition: a qualitative interview study of the experiences of advanced cancer patients and their families. Clin Nutr 2005; 24(6):961-970.

(274) Malone M, Howard L. Long-term hyperalimentation. Curr Opin Gastroenterol 1994; 10:227-234.

(275) Ireton-Jones C, DeLegge M. Home parenteral nutrition registry: a five-year retrospective evaluation of outcomes of patients receiving home parenteral nutrition support. Nutrition 2005; 21(2):156-160.

(276) Dudrick SJ, Groff DB, Wilmore DW. Long term venous catheterization in infants. Surg Gynecol Obstet 1969; 129(4):805-808.

(277) Howard L, Ashley C. Management of complications in patients receiving home parenteral nutrition. Gastroenterology 2003; 124(6):1651-1661.

(278) Schuman ES, Winters V, Gross GF, Hayes JF. Management of Hickman catheter sepsis. Am J Surg 1985; 149(5):627-628.

(279) Buchman AL, Moukarzel A, Goodson B, Herzog F, Pollack P, Reyen L et al. Catheter-related infections associated with home parenteral nutrition and

predictive factors for the need for catheter removal in their treatment. JPEN J Parenter Enteral Nutr 1994; 18(4):297-302.

(280) Green CJ, Mountford V, Hamilton H, Kettlewell MG, Travis SP. A 15-year audit of home parenteral nutrition provision at the John Radcliffe Hospital, Oxford. QJM 2008; 101(5):365-369.

(281) Freshwater DA, Saadeddin A, Deel-Smith P, Digger T, Jones BJ. Can home parenteral nutrition be provided by non-specialised centres? 2300 weeks of experience at a district general hospital in the United Kingdom. Clin Nutr 2005; 24(2):229-235.

(282) Marra AR, Opilla M, Edmond MB, Kirby DF. Epidemiology of bloodstream infections in patients receiving long-term total parenteral nutrition. J Clin Gastroenterol 2007; 41(1):19-28.

(283) Saqui O, Raman M, Chang A, Allard JP. Canadian home total parenteral nutrition program: a prospective study using US Centers for Disease Control and Prevention criteria. J Assoc Vascular Access 2007; 12:85-88.

(284) Moukarzel AA, Haddad I, Ament ME, Buchman AL, Reyen L, Maggioni A et al. 230 patient years of experience with home long-term parenteral nutrition in childhood: natural history and life of central venous catheters. J Pediatr Surg 1994; 29(10):1323-1327.

(285) Candusso M, Giglio L, Faraguna D. 100 PT/YR pediatric home parenteral nutrition experience. Transplant Proc 1997; 29(3):1864-1865.

(286) Diamanti A, Basso MS, Castro M, Calce A, Pietrobattista A, Gambarara M. Prevalence of life-threatening complications in pediatric patients affected by intestinal failure. Transplant Proc 2007; 39(5):1632-1633.

(287) Candusso M, Faraguna D, Dileo G, Loganes C. Home parenteral nutrition in children: outcomes and quality of life. Clin Nutr 2001; 20 Suppl 2:7-10.

(288) Werlin SL, Lausten T, Jessen S, Toy L, Norton A, Dallman L et al. Treatment of central venous catheter occlusions with ethanol and hydrochloric acid. JPEN J Parenter Enteral Nutr 1995; 19(5):416-418.

(289) Howard L, Alger S, Michalek A, Heaphey L, Aftahi S, Johnston K. Home Parenteral Nutrition. In: Rombeau JL, Caldwell MD, editors. Parenteral Nutrition. Philadelphia: WB Saunders, 1993: 814-839.

(290) Davis EF. Upper extremity venous thrombi and central venous catheters. Crit Care Burse 1991; 11:16-22.

(291) Kelly DA. Liver complications of pediatric parenteral nutrition--epidemiology. Nutrition 1998; 14(1):153-157.

(292) Stanko RT, Nathan G, Mendelow H, Adibi SA. Development of hepatic cholestasis and fibrosis in patients with massive loss of intestine supported by prolonged parenteral nutrition. Gastroenterology 1987; 92(1):197-202.

(293) Bowyer BA, Fleming CR, Ludwig J, Petz J, McGill DB. Does long-term home parenteral nutrition in adult patients cause chronic liver disease? JPEN J Parenter Enteral Nutr 1985; 9(1):11-17.

(294) Buchman AL, Ament M. Liver disease and total parenteral nutrition. In: Zakim TD, editor. Textbook of Hepatology. Philadelphia: Saunders, 1996: 1810-1821.

(295) Briones ER, Iber FL. Liver and biliary tract changes and injury associated with total parenteral nutrition: pathogenesis and prevention. J Am Coll Nutr 1995; 14(3):219-228.

(296) Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med 2000; 132(7):525-532.

(297) Quigley EM, Marsh MN, Shaffer JL, Markin RS. Hepatobiliary complications of total parenteral nutrition. Gastroenterology 1993; 104(1):286-301.

(298) Clarke PJ, Ball MJ, Kettlewell MG. Liver function tests in patients receiving parenteral nutrition. JPEN J Parenter Enteral Nutr 1991; 15(1):54-59.

(299) Messing B, Colombel JF, Heresbach D, Chazouilleres O, Galian A. Chronic cholestasis and macronutrient excess in patients treated with prolonged parenteral nutrition. Nutrition 1992; 8(1):30-36.

(300) Ito Y, Shils ME. Liver dysfunction associated with long-term total parenteral nutrition in patients with massive bowel resection. JPEN J Parenter Enteral Nutr 1991; 15(3):271-276.

(301) Beale EF, Nelson RM, Bucciarelli RL, Donnelly WH, Eitzman DV. Intrahepatic cholestasis associated with parenteral nutrition in premature infants. Pediatrics 1979; 64(3):342-347.

(302) Suita S, Ikeda K, Nagasaki A, Hayashida Y, Kaneko T, Hamano Y et al. Follow-up studies of children treated with a long-term intravenous nutrition (IVN) during the neonatal period. J Pediatr Surg 1982; 17(1):37-42.

(303) Ferrone M, Geraci M. A review of the relationship between parenteral nutrition and metabolic bone disease. Nutr Clin Pract 2007; 22(3):329-339.

(304) Hurley DL, McMahon MM. Long-term parenteral nutrition and metabolic bone disease. Endocrinol Metab Clin North Am 1990; 19(1):113-131.

(305) Pironi L, Labate AM, Pertkiewicz M, Przedlacki J, Tjellesen L, Staun M et al. Prevalence of bone disease in patients on home parenteral nutrition. Clin Nutr 2002; 21(4):289-296.

(306) Cohen-Solal M, Baudoin C, Joly F, Vahedi K, D'Aoust L, De Vernejoul MC et al. Osteoporosis in patients on long-term home parenteral nutrition: a longitudinal study. J Bone Miner Res 2003; 18(11):1989-1994.

(307) Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F et al. ESPEN Guidelines on Parenteral Nutrition: home parenteral nutrition (HPN) in adult patients. Clin Nutr 2009; 28(4):467-479.

(308) Buchman AL, Moukarzel A. Metabolic bone disease associated with total parenteral nutrition. Clin Nutr 2000; 19(4):217-231.

(309) Buchman AL, Moukarzel A, Ament ME, Gornbein J, Goodson B, Carlson C et al. Serious renal impairment is associated with long-term parenteral nutrition. JPEN J Parenter Enteral Nutr 1993; 17(5):438-444.

(310) Idoate MA, Martinez AJ, Bueno J, Abu-Elmagd K, Reyes J. The neuropathology of intestinal failure and small bowel transplantation. Acta Neuropathol 1999; 97(5):502-508.

(311) Koo WW. Parenteral nutrition-related bone disease. JPEN J Parenter Enteral Nutr 1992; 16(4):386-394.

(312) Sax HC, Bower RH. Hepatic complications of total parenteral nutrition. JPEN J Parenter Enteral Nutr 1988; 12(6):615-618.

(313) Pironi L, Miglioli M, Ruggeri E, Longo N, Suriani U, Maselli S et al. Home parenteral nutrition for the management of chronic intestinal failure: a 34 patient-year experience. Ital J Gastroenterol 1993; 25(8):411-418.

(314) Geertsma MA, Hyams JS, Pelletier JM, Reiter S. Feeding resistance after parenteral hyperalimentation. Am J Dis Child 1985; 139(3):255-256.

(315) Handen BL, Mandell F, Russo DC. Feeding induction in children who refuse to eat. Am J Dis Child 1986; 140(1):52-54.

(316) Forchielli ML, Richardson D, Folkman J, Gura K, Lo CW. Better living through chemistry, constant monitoring, and prompt interventions: 26 years on home parenteral nutrition without major complications. Nutrition 2008; 24(1):103-107.

(317) Fairman J, Compher C, Morris J, Mullen JL. Living long with short bowel syndrome: a historical case of twenty-nine years of living with home parenteral nutrition. JPEN J Parenter Enteral Nutr 2007; 31(2):127-134.

(318) Versleijen M, Vissers R, Wanten G. Excellent quality of life after 31 years of parenteral nutrition via an arteriovenous fistula. Eur J Clin Nutr 2008; 62(10):1253-1254.

(319) Howard L. Home parenteral nutrition: a transatlantic view. Clin Nutr 1999; 18(3):131-133.

(320) Messing B, Lemann M, Landais P, Gouttebel MC, Gerard-Boncompain M, Saudin F et al. Prognosis of patients with nonmalignant chronic intestinal failure receiving long-term home parenteral nutrition. Gastroenterology 1995; 108(4):1005-1010.

(321) Elia M. An international perspective on artificial nutritional support in the community. Lancet 1995; 345(8961):1345-1349.

(322) Richards DM, Irving MH. Cost-utility analysis of home parenteral nutrition. Br J Surg 1996; 83(9):1226-1229.

(323) Wesley JR. Home parenteral nutrition: indications, principles, and cost-effectiveness. Compr Ther 1983; 9(4):29-36.

(324) Wateska LP, Sattler LL, Steiger E. Cost of a home parenteral nutrition program. JAMA 1980; 244(20):2303-2304.

(325) Dzierba SH, Mirtallo JM, Grauer DW, Schneider PJ, Latiolais CJ, Fabri PJ. Fiscal and clinical evaluation of home parenteral nutrition. Am J Hosp Pharm 1984; 41(2):285-291.

(326) Baptista RJ, Lahey MA, Bistrian BR, Champagne CD, Miller DG, Kelly SE et al. Periodic reassessment for improved, cost-effective care in home total parenteral nutrition: a case report. JPEN J Parenter Enteral Nutr 1984; 8(6):708-710.

(327) Reddy P, Malone M. Cost and outcome analysis of home parenteral and enteral nutrition. JPEN J Parenter Enteral Nutr 1998; 22(5):302-310.

(328) Detsky AS, McLaughlin JR, Abrams HB, Whittaker JS, Whitwell J, L'Abbe K et al. A cost-utility analysis of the home parenteral nutrition program at Toronto General Hospital: 1970-1982. JPEN J Parenter Enteral Nutr 1986; 10(1):49-57.

(329) Tu Duy Khiem-El Aatmani, Senesse P, Reimund JM, Beretz L, Baumann R, Pinguet F. Home Parenteral Nutrition: a direct costs study in the approved centres of Montpellier and Strasbourg. Gastroenterol Clin Biol 2006; 30(4):574-579.

(330) Colomb V. Economic aspects of paediatric home parenteral nutrition. Curr Opin Clin Nutr Metab Care 2000; 3(3):237-239.

(331) Puntis JW. The economics of home parenteral nutrition. Nutrition 1998; 14(10):809-812.

(332) Longworth L, Young T, Beath SV, Kelly DA, Mistry H, Protheroe SM et al. An economic evaluation of pediatric small bowel transplantation in the United Kingdom. Transplantation 2006; 82(4):508-515.

(333) Melville CA, Bisset WM, Long S, Milla PJ. Counting the cost: hospital versus home central venous catheter survival. J Hosp Infect 1997; 35(3):197-205.

(334) Masetti M, Cautero N, Lauro A, Di Benedetto F, Begliomini B, Siniscalchi A et al. Three-year experience in clinical intestinal transplantation. Transplant Proc 2004; 36(2):309-311.

(335) DiMartini A, Fitzgerald MG, Magill J, Funovitz M, Abu-Elmagd K, Furukawa H et al. Psychiatric evaluations of small intestine transplantation patients. Gen Hosp Psychiatry 1996; 18(6 Suppl):25S-29S.

(336) Lillehei RC, Idezuki Y, Feemster JA, Dietzman RH, Kelly WD, Merkel FK et al. Transplantation of stomach, intestine, and pancreas: experimental and clinical observations. Surgery 1967; 62(4):721-741.

(337) Fishbein TM, Gondolesi GE, Kaufman SS. Intestinal transplantation for gut failure. Gastroenterology 2003; 124(6):1615-1628.

(338) Todo S, Tzakis A, Reyes J, Abu-Elmagd K, Casavilla A, Nour BM et al. Clinical small bowel or small bowel plus liver transplantation under FK 506. Transplant Proc 1991; 23(6):3093-3095.

(339) Grant D. Intestinal transplantation: 1997 report of the international registry. Intestinal Transplant Registry. Transplantation 1999; 67(7):1061-1064.

(340) Beath SV, Protheroe SP, Brook GA, Kelly DA, McKiernan PJ, Murphy MS et al. Early experience of paediatric intestinal transplantation in the United Kingdom, 1993 to 1999. Transplant Proc 2000; 32(6):1225.

(341) Beath SV, Booth IW, Murphy MS, Buckels JA, Mayer AD, McKiernan PJ et al. Nutritional care and candidates for small bowel transplantation. Arch Dis Child 1995; 73(4):348-350.

(342) Kaufman SS, Atkinson JB, Bianchi A, Goulet OJ, Grant D, Langnas AN et al. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Pediatr Transplant 2001; 5(2):80-87.

(343) Care routines following pediatric intestine transplantation. International Symposium on Intestine Transplantation; Cambridge UK: 1997.

(344) Tarbell SE, Kosmach B. Parental psychosocial outcomes in pediatric liver and/or intestinal transplantation: pretransplantation and the early postoperative period. Liver Transpl Surg 1998; 4(5):378-387.

(345) Farmer DG, McDiarmid SV, Yersiz H, Cortina G, Amersi F, Vargas J et al. Outcome after intestinal transplantation: results from one center's 9-year experience; discussion 1031-2. Arch Surg 2001; 136(9):1027-1031.

(346) Pironi L, Hebuterne X, Van Gossum A, Messing B, Lyszkowska M, Colomb V et al. Candidates for intestinal transplantation: a multicenter survey in Europe. Am J Gastroenterol 2006; 101(7):1633-1643.

(347) Goulet O, Ruemmele F. Causes and management of intestinal failure in children. Gastroenterology 2006; 130(2 Suppl 1):S16-S28.

(348) Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument (WHOQOL). Qual Life Res 1993; 2(2):153-159.

(349) Edlund M, Tancredi LR. Quality of life: an ideological critique. Perspect Biol Med 1985; 28(4):591-607.

(350) A study of the medical needs of recipients of old age assistance in New York City in 1934. 1937.

(351) Eisenberg HS, Goldenberg IS. A measurement of quality of survival of breasr cancer patients. In: Hayward JL, Bullbrook RP, editors. Clinical evaluation in breast cancer. London: Academic Press, 1966.

(352) Carlens E, Dahlstrom G, Nou E. Comparative measurements of quality of survival of lung cancer patients after diagnosis. Scand J Respir Dis 1970; 51(4):268-275.

(353) Tofler OB. Life units. A discussion in the Department of Cardiology, Royal Perth Hospital, Australia. Br Heart J 1970; 32(6):771-773.

(354) Priestman TJ, Baum M. Evaluation of quality of life in patients receiving treatment for advanced breast cancer. Lancet 1976; 1(7965):899-900.

(355) Croog SH, Levine S, Testa MA, Brown B, Bulpitt CJ, Jenkins CD et al. The effects of antihypertensive therapy on the quality of life. N Engl J Med 1986; 314(26):1657-1664.

(356) Flanagan JC. Measurement of quality of life: current state of the art. Arch Phys Med Rehabil 1982; 63(2):56-59.

(357) Weinberger M, Oddone EZ, Samsa GP, Landsman PB. Are health-related quality-of-life measures affected by the mode of administration? J Clin Epidemiol 1996; 49(2):135-140.

(358) Fallowfield L. Quality of quality-of-life data. Lancet 1996; 348(9025):421-422.

(359) Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ 1993; 306(6890):1437-1440.

(360) Borgaonkar MR, Irvine EJ. Quality of life measurement in gastrointestinal and liver disorders. Gut 2000; 47(3):444-454.

(361) Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993; 118(8):622-629.

(362) Varni J, Seid M, Kurtin PS. Pediatric Health Related Quality of Life Measurement Technology: A guide for Health Care Decision Makers. JCOM 1999; 6(4):33-40.

(363) Eiser C, Morse R. The measurement of quality of life in children: past and future perspectives. J Dev Behav Pediatr 2001; 22(4):248-256.

(364) Lansky LL, List MA, Lansky SB, Cohen ME, Sinks LF. Toward the development of a play performance scale for children (PPSC). Cancer 1985; 56(7 Suppl):1837-1840.

(365) Eiser C, Mohay H, Morse R. The measurement of quality of life in young children. Child Care Health Dev 2000; 26(5):401-414.

(366) Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. Arch Dis Child 2001; 84(3):205-211.

(367) Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Qual Life Res 2001; 10(4):347-357.

(368) Patient-reported outcome and quality of life instruments database. http://www.qolid.org/proqolid/about_proqolid. 2008.

(369) Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30(6):473-483.

(370) Rentz AM, Battista C, Trudeau E, Jones R, Robinson P, Sloan S et al. Symptom and health-related quality-of-life measures for use in selected gastrointestinal disease studies: a review and synthesis of the literature. Pharmacoeconomics 2001; 19(4):349-363.

(371) Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. J Epidemiol Community Health 1999; 53(1):46-50.

(372) Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67(6):361-370.

(373) Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. J Psychosom Res 1997; 42(1):17-41.

(374) Crawford JR, Henry JD, Crombie C, Taylor EP. Normative data for the HADS from a large non-clinical sample. Br J Clin Psychol 2001; 40(Pt 4):429-434.

(375) EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990; 16(3):199-208.

(376) Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 1998; 316(7133):736-741.

(377) Kuster PA, Badr LK, Chang BL, Wuerker AK, Benjamin AE. Factors influencing health promoting activities of mothers caring for ventilator-assisted children. J Pediatr Nurs 2004; 19(4):276-287.

(378) Folkman S, Lazarus R. Ways of coping questionnaire, sampler set, manual, test booklet, scoring key. Ways of coping questionnaire, sampler set, manual, test booklet, scoring key. Consulting Psychologists Press, 1988: 1-34.

(379) Knussen C, Sloper P, Cunningham CC, Turner S. The use of the Ways of Coping (Revised) questionnaire with parents of children with Down's syndrome. Psychol Med 1992; 22(3):775-786.

(380) Dunn ME, Burbine T, Bowers CA, Tantleff-Dunn S. Moderators of stress in parents of children with autism. Community Ment Health J 2001; 37(1):39-52.

(381) Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O et al. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol Med 1997; 27(1):191-197.

(382) Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. Psychol Med 1979; 9(1):139-145.

(383) Stein RE, Jessop DJ. Functional status II(R). A measure of child health status. Med Care 1990; 28(11):1041-1055.

(384) Miller IW, Bishop DS, Epstein NB, Keitner GL. The McMaster Family Assessment Device: Reliability and Validity. Journal of Marital and Family Therapy 1985; 11(4):345-356.

(385) Farmer RG, Easley KA, Farmer JM. Quality of life assessment by patients with inflammatory bowel disease. Cleve Clin J Med 1992; 59(1):35-42.

(386) Price BS, Levine EL. Permanent total parenteral nutrition: psychological and social responses of the early stages. JPEN J Parenter Enteral Nutr 1979; 3(2):48-52.

(387) Ladefoged K. Quality of life in patients on permanent home parenteral nutrition. JPEN J Parenter Enteral Nutr 1981; 5(2):132-137.

(388) Detsky AS, McLaughlin JR, Abrams HB, L'Abbe KA, Whitwell J, Bombardier C et al. Quality of life of patients on long-term total parenteral nutrition at home. J Gen Intern Med 1986; 1(1):26-33.

(389) Stokes MA, Almond DJ, Pettit SH, Mughal MM, Turner M, Shaffer JL et al. Home parenteral nutrition: a review of 100 patient years of treatment in 76 consecutive cases. Br J Surg 1988; 75(5):481-483.

(390) Burnes JU, O'Keefe SJ, Fleming CR, Devine RM, Berkner S, Herrick L. Home parenteral nutrition--a 3-year analysis of clinical and laboratory monitoring. JPEN J Parenter Enteral Nutr 1992; 16(4):327-332.

(391) Price BS, Levine EL. Permanent total parenteral nutrition: psychological and social responses of the early stages. JPEN J Parenter Enteral Nutr 1979; 3(2):48-52.

(392) Smith CE. Quality of life in long-term total parenteral nutrition patients and their family caregivers. JPEN J Parenter Enteral Nutr 1993; 17(6):501-506.

(393) Richards DM, Scott NA, Shaffer JL, Irving M. Opiate and sedative dependence predicts a poor outcome for patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr 1997; 21(6):336-338.

(394) Egger NG, Carlson GL, Shaffer JL. Nutritional status and assessment of patients on home parenteral nutrition: anthropometry, bioelectrical impedance, or clinical judgment? Nutrition 1999; 15(1):1-6.

(395) Jamieson CP, Norton B, Day T, Lakeman M, Powell-Tuck J. The quantitative effect of nutrition support on quality of life in outpatients. Clinical Nutrition 1997; 16:25-28.

(396) Richards DM, Irving MH. Assessing the quality of life of patients with intestinal failure on home parenteral nutrition. Gut 1997; 40(2):218-222.

(397) Galandiuk S, O'Neill M, McDonald P, Fazio VW, Steiger E. A century of home parenteral nutrition for Crohn's disease. Am J Surg 1990; 159(6):540-544.

(398) Cameron EA, Binnie JA, Jamieson NV, Pollard S, Middleton SJ. Quality of life in adults following small bowel transplantation. Transplant Proc 2002; 34(3):965-966.

(399) Carlsson E, Bosaeus I, Nordgren S. Quality of life and concerns in patients with short bowel syndrome. Clin Nutr 2003; 22(5):445-452.

(400) Chambers A, Hennessy E, Powell-Tuck J. Longitudinal trends in quality of life after starting home parenteral nutrition: a randomised controlled study of telemedicine. Clin Nutr 2006; 25(3):505-514.

(401) Pironi L, Paganelli F, Labate AM, Merli C, Guidetti C, Spinucci G et al. Safety and efficacy of home parenteral nutrition for chronic intestinal failure: a 16-year experience at a single centre. Dig Liver Dis 2003; 35(5):314-324.

(402) Smith CE, Curtas S, Kleinbeck SV, Werkowitch M, Mosier M, Seidner DL et al. Clinical trial of interactive and videotaped educational interventions reduce infection, reactive depression, and rehospitalizations for sepsis in patients on home parenteral nutrition. JPEN J Parenter Enteral Nutr 2003; 27(2):137-145.

(403) Cuerda C, Camblor M, Breton I, Garcia-Peris P. Long-term follow-up of home parenteral nutrition at a general hospital: complications and quality of life. Nutr Hosp 2002; 17(1):15-21.

(404) Jeppesen PB, Langholz E, Mortensen PB. Quality of life in patients receiving home parenteral nutrition. Gut 1999; 44(6):844-852.

(405) Rovera GM, DiMartini A, Schoen RE, Rakela J, Abu-Elmagd K, Graham TO. Quality of life of patients after intestinal transplantation. Transplantation 1998; 66(9):1141-1145.

(406) DiMartini A, Rovera GM, Graham TO, Furukawa H, Todo S, Funovits M et al. Quality of life after small intestinal transplantation and among home parenteral nutrition patients. JPEN J Parenter Enteral Nutr 1998; 22(6):357-362.

(407) Ferrans CE, Powers MJ. Quality of life index: development and psychometric properties. ANS Adv Nurs Sci 1985; 8(1):15-24.

(408) de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. Br J Cancer 1990; 62(6):1034-1038.

(409) Baxter JP, Fayers PM, McKinlay AW. A review of the instruments used to assess the quality of life of adult patients with chronic intestinal failure receiving parenteral nutrition at home. Br J Nutr 2005; 94(5):633-638.

(410) Baxter JP, Fayers PM, McKinlay AW. The clinical and psychometric validation of a questionnaire to assess the quality of life of adult patients treated with long-term parenteral nutrition. JPEN J Parenter Enteral Nutr 2010; 34(2):131-142.

(411) Jeppesen PB, Staun M, Mortensen PB. Adult patients receiving home parenteral nutrition in Denmark from 1991 to 1996: who will benefit from intestinal transplantation? Scand J Gastroenterol 1998; 33(8):839-846.

(412) Van Gossum A, Vahedi K, Abdel M, Staun M, Pertkiewicz M, Shaffer J et al. Clinical, social and rehabilitation status of long-term home parenteral nutrition patients: results of a European multicentre survey. Clin Nutr 2001; 20(3):205-210.

(413) Meyer KB, Espindle DM, DeGiacomo JM, Jenuleson CS, Kurtin PS, Davies AR. Monitoring dialysis patients' health status. Am J Kidney Dis 1994; 24(2):267-279.

(414) Malone M. Longitudinal assessment of outcome, health status, and changes in lifestyle associated with long-term home parenteral and enteral nutrition. JPEN J Parenter Enteral Nutr 2002; 26(3):164-168.

(415) Iwarzon M, Gardulf A, Lindberg G. Quality of life of patients with chronic intestinal pseudo-obstruction. Gastroenterology 2000; 118(4):5416.

(416) Chambers A, Greig E, Powell-Tuck J. Quality of life in chronic idiopathic intestinal pseudo-obstruction. Gut 2004; 53:289.

(417) Iwarzon M, Gardulf A, Lindberg G. Functional status, health-related quality of life and symptom severity in patients with chronic intestinal pseudo-obstruction and enteric dysmotility. Scand J Gastroenterol 2009; 44(6):700-707.

(418) Lapointe R. Chronic Idiopathic Intestinal Pseudo-obstruction Treated by Near Total Small Bowel Resection: A 20-Year Experience. J Gastrointest Surg 2010.

(419) Farmer RG, Michener WM. Prognosis of Crohn's disease with onset in childhood or adolescence. Dig Dis Sci 1979; 24(10):752-757.

(420) Farmer RG, Whelan G, Fazio VW. Long-term follow-up of patients with Crohn's disease. Relationship between the clinical pattern and prognosis. Gastroenterology 1985; 88(6):1818-1825.

(421) Amarnath RP, Fleming CR, Perrault J. Home parenteral nutrition in chronic intestinal diseases: its effect on growth and development. J Pediatr Gastroenterol Nutr 1987; 6(1):89-95.

(422) O'Connor MJ, Ralston CW, Ament ME. Intellectual and perceptual-motor performance of children receiving prolonged home total parenteral nutrition. Pediatrics 1988; 81(2):231-236.

(423) Leonberg BL, Chuang E, Eicher P, Tershakovec AM, Leonard L, Stallings VA. Long-term growth and development in children after home parental nutrition. J Pediatr 1998; 132(3 Pt 1):461-466.

(424) Murphy RL, Block P, Bird KT, Yurchak P. Accuracy of cardiac auscultation by microwave. Chest 1973; 63(4):578-581.

(425) Zundel KM. Telemedicine: history, applications, and impact on librarianship. Bull Med Libr Assoc 1996; 84(1):71-79.

(426) Feigin RD, Cherry JD, Demmler GJ, Kaplan SL. Textbook of Pediatric Infectious Diseases. 5 ed. Pennsylvania: Sanders, 2004.

(427) Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut 2000; 46(6):813-818.

(428) Schneidera SM, Pouget I, Staccini P, Rampal P, Hebuterne X. Quality of life in long-term home enteral nutrition patients. Clinical Nutrition 2000; 19(1):23-28.

(429) McRorie J, Zorich N, Riccardi K, Bishop L, Filloon T, Wason S et al. Effects of olestra and sorbitol consumption on objective measures of diarrhea: impact of stool viscosity on common gastrointestinal symptoms. Regul Toxicol Pharmacol 2000; 31(1):59-67.

(430) Hearing SD, Thomas LA, Heaton KW, Hunt L. Effect of cholecystectomy on bowel function: a prospective, controlled study. Gut 1999; 45(6):889-894.

(431) Coletta M, Di Palma L, Tomba C, Basilisco G. Discrepancy between recalled and recorded bowel habits in irritable bowel syndrome. Aliment Pharmacol Ther 2010; 32(2):282-288.

(432) Manning AP, Wyman JB, Heaton KW. How trustworthy are bowel histories? Comparison of recalled and recorded information. Br Med J 1976; 2(6029):213-214.

(433) Heaton KW, Radvan J, Cripps H, Mountford RA, Braddon FE, Hughes AO. Defecation frequency and timing, and stool form in the general population: a prospective study. Gut 1992; 33(6):818-824.

(434) Avill R, Mangnall YF, Bird NC, Brown BH, Barber DC, Seagar AD et al. Applied potential tomography. A new noninvasive technique for measuring gastric emptying. Gastroenterology 1987; 92(4):1019-1026.

(435) Akkermans LM, van Isselt JW. Gastric motility and emptying studies with radionuclides in research and clinical settings. Dig Dis Sci 1994; 39(12 Suppl):95S-96S.

(436) Vantrappen G. Methods to study gastric emptying. Dig Dis Sci 1994; 39(12 Suppl):91S-94S.

(437) Petrie A, Sabin C. Medical Statistics at a Glance. 1st Edition ed. Blackwell Science, 2000.

(438) Howard LJ. Length of life and quality of life on home parenteral nutrition. JPEN J Parenter Enteral Nutr 2002; 26(5 Suppl):S55-S59.

(439) Fayers PM, Machin D. Quality of Life. Assessment, analysis and interptretation. West Sussex, England: John Wiley & Sons Ltd., 2000.

(440) Blazeby J, Sprangers M, Cull A, Groenvold M, Bottomley A. EORTC quality of life group guidelines for developing questionnaire modules. 3rd ed. Brussels: 2002.

(441) Chambers A, Powell-Tuck J. Determinants of quality of life in home parenteral nutrition. Curr Opin Clin Nutr Metab Care 2007; 10(3):318-323.

(442) Baxter JP, Fayers PM, McKinlay AW. The Clinical and Psychometric Validation of a Questionnaire to Assess the Quality of Life of Adult Patients Treated With Long-Term Parenteral Nutrition. JPEN J Parenter Enteral Nutr 2009.

(443) Lawoko S, Soares JJ. Quality of life among parents of children with congenital heart disease, parents of children with other diseases and parents of healthy children. Qual Life Res 2003; 12(6):655-666.

(444) Macdonald-Brown AJ. General practitioner prescribing of total parenteral nutrition at home. J R Coll Gen Pract 1986; 36(286):222.

(445) Vantini I, Benini L, Bonfante F, Talamini G, Sembenini C, Chiarioni G et al. Survival rate and prognostic factors in patients with intestinal failure. Dig Liver Dis 2004; 36(1):46-55.

(446) Jones BJ. Abstracts of the Nutrition Society meetings of November 2001 and February 2002 -Home parenteral Nutrition: Ensuring Equity of care. Proc Nutr Soc 2002; 61:1A-62A.

(447) Brady C. New models for OP management. Clinical Nutrition 2002; 21(Supplement 1):123-125.

(448) Dormandy E, Brown K, Reid EP, Marteau TM. Towards socially inclusive research: an evaluation of telephone questionnaire administration in a multilingual population. BMC Med Res Methodol 2008; 8:2.

(449) Hodgkinson R, Lester H. Stresses and coping strategies of mothers living with a child with cystic fibrosis: implications for nursing professionals. J Adv Nurs 2002; 39(4):377-383.

(450) Northam E, Anderson P, Adler R, Werther G, Warne G. Psychosocial and family functioning in children with insulin-dependent diabetes at diagnosis and one year later. J Pediatr Psychol 1996; 21(5):699-717.

(451) Osman LM, Baxter-Jones AD, Helms PJ. Parents' quality of life and respiratory symptoms in young children with mild wheeze. EASE Study Group. Eur Respir J 2001; 17(2):254-258.

(452) Lam P, Hiscock H, Wake M. Outcomes of infant sleep problems: a longitudinal study of sleep, behavior, and maternal well-being. Pediatrics 2003; 111(3):e203-e207.

(453) Alonso EM, Neighbors K, Barton FB, McDiarmid SV, Dunn SP, Mazariegos GV et al. Health-related quality of life and family function following pediatric liver transplantation. Liver Transpl 2008; 14(4):460-468.

(454) Unlu G, Aras S, Guvenir T, Buyukgebiz B, Bekem O. [Family functioning, personality disorders, and depressive and anxiety symptoms in the mothers of children with food refusal]. Turk Psikiyatri Derg 2006; 17(1):12-21.

(455) Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005; 41 Suppl 2:S1-87.

(456) Elia M, Russell C, Shaffer J, Micklewright A, Wood S, Wheatley C et al. Annual Report of the British Artificial Nutrition Survey. 2000.

(457) Howard L, Malone M. Clinical outcome of geriatric patients in the United States receiving home parenteral and enteral nutrition. Am J Clin Nutr 1997; 66(6):1364-1370.

(458) Baxter JP, Fayers PM, McKinlay AW. The development and translation of a treatment-specific quality of life questionnaire for adult patients on home parenteral nutrition. The European e-Journal of Clinical Nutrition and Metabolism 2008; 3(1):e22-e28.

(459) Pinnock H, Juniper EF, Sheikh A. Concordance between supervised and postal administration of the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) and Asthma Control Questionnaire (ACQ) was very high. J Clin Epidemiol 2005; 58(8):809-814.

(460) Weinberger M, Oddone EZ, Samsa GP, Landsman PB. Are health-related quality-of-life measures affected by the mode of administration? J Clin Epidemiol 1996; 49(2):135-140.

Appendices

Material which examiners are not required to read in order to examine the thesis, but to which they may refer if they wish.

Appendix 1

Short Form 36 (SF36) Questionnaire (telephone script)

These first questions are about your health now and your current daily activities.

Q1 (GH)
In general would you say your health is…

Excellent (5.0)	
Very Good (4.4)	
Good (3.4)	
Fair (2.0)	
Poor (1.0)	

Q2 (HT)
Compared to 1 year ago, how would you rate your health in general now? Would you say it is…

Much better than 1 year ago (1)	
Somewhat better now than 1 year ago (2)	
About the same as 1 year ago (3)	
Somewhat worse than 1 year ago (4)	
Much worse than 1 year ago (5)	

Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if your health now limits you a lot, limits you a little, or does not limit you at all in these activities

Q3 (PF)
First vigorous activities, such as running, lifting heavy objects or participating in strenuous sports. Does your health now limit you a lot, limit you a little or not limit you at all?
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

Q4 (PF)
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf. Does your health now limit you a lot, limit you a little, or not limit you at all.
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

Q5 (PF)
Lifting or carrying groceries. Does your health now limit you a lot, limit you a little, or not limit you at all?
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

Q6 (PF)
Climbing several flights of stairs. Does your health now limit you a lot, limit you a little, or not limit you at all?
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

Q7 (PF)
Climbing one flight of stairs. Does your health now limit you a lot, limit you a little, or not limit you at all?
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

Q8 (PF)
Bending kneeling or stooping. Does your health now limit you a lot, limit you a little, or not limit you at all?
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

Q9 (PF)
Walking more than one mile. Does your health now limit you a lot, limit you a little, or not limit you at all?
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

Q10 (PF)
Walking half a mile. Does your health now limit you a lot, limit you a little, or not limit you at all?
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

Q11 (PF)
Walking 100 yards. Does your health now limit you a lot, limit you a little, or not limit you at all?
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

Q12 (PF)
Bathing or dressing yourself. Does your health now limit you a lot, limit you a little, or not limit you at all
If respondent replies they don't do that activity ask: Is that because of your health?

Yes, limited a lot (1)	
Yes, limited a little (2)	
No, not limited at all (3)	

The following 4 questions ask you about your physical health and your daily activities:

Q13 (RP)
During the past 4 weeks, have you had to cut down on the amount of time you spent on work or any other regular activities as a result of your physical health?

Yes (1)	
No (2)	

Q14 (RP)
During the past 4 weeks, have you accomplished less than you would like as a result of your physical health?

Yes (1)	
No (2)	

Q15 (RP)
During the past 4 weeks, were you limited in the kind of work or other regular daily activities as a result of your physical health, for example, it took extra effort?

Yes (1)	
No (2)	

Q16 (RP)
During the last 4 weeks have you had difficulty performing work or other regular daily activities as a result of your physical health, for example it took extra effort?

Yes (1)	
No (2)	

The following 3 questions ask you about your emotions and your daily activities:

Q17 (RE)
During the past 4 weeks, have you cut down on the amount of time you spent on work or regular daily activities as a result of any emotional problems, such as feeling depressed or anxious?

Yes (1)	
No (2)	

Q18 (RE)
During the past 4 weeks, have you accomplished less than you would like as a result of any emotional problems, such as feeling depressed or anxious?

Yes (1)	
No (2)	

Q19 (RE)
During the past 4 weeks, did you not do work or other regular daily activities as carefully as usual as a result of any emotional problems, such as feeling depressed or anxious?

Yes (1)	
No (2)	

Q20 (SF)
During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities like visiting friends or relatives? Has it interfered…

Not at all (5)	
Slightly (4)	
Moderately (3)	
Quite a bit (2)	
Or Extremely (1)	

Q21 (BP)
During the past 4 weeks, how much did pain interfere with your normal work, including both outside the home and housework? Did it interfere…

Not at all (5)	
A little bit (4)	
Moderately (3)	
Quite a bit (2)	
Or Extremely (1)	

Q22 (BP)
How much bodily pain have you had during the past 4 weeks? Have you had…

None (6.0)	
Very mild (5.4)	
Mild (4.2)	
Moderate (3.1)	
Severe (2.2)	
Or very severe (1.0)	

Q23 (SF)
During the past 4 weeks, how much time has your physical health or emotional problems interfered with your physical activities like visiting with friends or relatives? Has it interfered…

All of the time (1)	
Most of the time (2)	
Some of the time (3)	
A little of the time (4)	
Or none of the time (5)	

The next questions are about how you feel and how things have been with you during the past 4 weeks. As I read each statement, please give me the one answer that comes closest to the way you have been feeling; is it all of the time, most of the time, a good bit of the time, some of the time, a little of the time or none of the time?

Q24 (VT)
How much of the time during the past 4 weeks…..did you feel full of life? Read categories.

All of the time (6)	
Most of the time (5)	
A good bit of the time (4)	
Some of the time (3)	
A little of the time (2)	
None of the time (1)	

Q25 (MH)
How much of the time during the past 4 weeks…..have you been a very nervous person? Read categories.

All of the time (1)	
Most of the time (2)	
A good bit of the time (3)	
Some of the time (4)	
A little of the time (5)	
None of the time (6)	

Q26 (MH)
How much of the time during the past 4 weeks…..have you felt so down in the dumps that nothing could cheer you up? Read categories only if necessary.

All of the time (1)	
Most of the time (2)	
A good bit of the time (3)	
Some of the time (4)	
A little of the time (5)	
None of the time (6)	

Q27 (MH)
How much of the time during the past 4 weeks…..have you felt calm and peaceful? Read categories only if necessary.

All of the time (6)	
Most of the time (5)	
A good bit of the time (4)	
Some of the time (3)	
A little of the time (2)	
None of the time (1)	

Q28 (VT)
How much of the time during the past 4 weeks…..did you have a lot of energy? Read categories only if necessary.

All of the time (6)	
Most of the time (5)	
A good bit of the time (4)	
Some of the time (3)	
A little of the time (2)	
None of the time (1)	

Q29 (MH)
How much of the time during the past 4 weeks…..have you felt downhearted and low? Read categories only if necessary.

All of the time (1)	
Most of the time (2)	
A good bit of the time (3)	
Some of the time (4)	
A little of the time (5)	
None of the time (6)	

Q30 (VT)
How much of the time during the past 4 weeks…..did you feel worn out? Read categories only if necessary.

All of the time (1)	
Most of the time (2)	
A good bit of the time (3)	
Some of the time (4)	
A little of the time (5)	
None of the time (6)	

Q31 (MH)
How much of the time during the past 4 weeks…..have you been a happy person? Read categories only if necessary.

All of the time (6)	
Most of the time (5)	
A good bit of the time (4)	
Some of the time (3)	
A little of the time (2)	
None of the time (1)	

Q32 (VT)
How much of the time during the past 4 weeks…..did you feel tired? Read categories only if necessary.

All of the time (1)	
Most of the time (2)	
A good bit of the time (3)	
Some of the time (4)	
A little of the time (5)	
None of the time (6)	

Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

Q33 (GH)
I seem to get ill a little easier than other people. Would you say that's….Read categories.

Definitely True (1)	
Mostly true (2)	
Don't Know (3) (don't read)	
Mostly false (4)	
Definitely false (5)	

Q34 (GH)
I am as healthy as anybody I know. Would you say that's….Read categories.

Definitely True (5)	
Mostly true (4)	
Don't Know (3) (don't read)	
Mostly false (2)	
Definitely false (1)	

Q35 (GH)
I expect my health to get worse. Would you say that's….Read categories.

Definitely True (1)	
Mostly true (2)	
Don't Know (3) (don't read)	
Mostly false (4)	
Definitely false (5)	

Q36 (GH)
My health is excellent. Would you say that's….Read categories.

Definitely True (5)	
Mostly true (4)	
Don't Know (3) (don't read)	
Mostly false (2)	
Definitely false (1)	

Appendix 2

Hospital Anxiety & Depression Scale (HADS) Questionnaire (telephone script)

The next 14 questions are about how you feel. As I read each statement please give me the one answer which comes closest to the way you have been feeling in the last week.
Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long thought out response.

Q1(A)
I feel tense or wound up;

Most of the time (3)	
A lot of the time (2)	
From time to time occasionally (1)	
Not at all (0)	

Q2 (D)
I still enjoy the things I used to enjoy;

Definitely as much (0)	
Not quite so much (1)	
Only a little (2)	
Hardly at all (3)	

Q3 (A)
I get a sort of frightened feeling as if something awful is about to happen;

Very Definitely and quite badly (3)	
Yes but not too badly (2)	
A little, but it doesn't worry me (1)	
Not at all (0)	

Q4 (D)
I can laugh and see the funny side of things;

As much as I always could (0)	
Not quite so much now (1)	
Definitely not so much now (2)	
Not at all (3)	

Q5 (A)
Worrying thoughts go through my head;

A great deal of the time (3)	
A lot of the time (2)	
From time to time but not too often (1)	
Only occasionally (0)	

Q6 (D)
I feel cheerful;

Not at all (3)	
Not often (2)	
Sometimes (1)	
Most of the time (0)	

Q7 (A)
I can sit at ease and feel relaxed;

Definitely (0)	
Usually (1)	
Not often (2)	
Not at all (3)	

Q8 (D)
I feel as if I am slowed down;

Nearly all the time (3)	
Very often (2)	
Sometimes (1)	
Not at all (0)	

Q9 (A)
I get a sort of frightened feeling like “butterflies” in the stomach;

Not at all (0)	
Occasionally (1)	
Quite often (2)	
Very Often (3)	

Q10 (D)
I have lost interest in my appearance;

Definitely (3)	
I don’t take so much care as I should (2)	
I may not take quite as much care (1)	
I take just as much care as ever (0)	

Q11 (A)
I feel restless as if I have to be on the move;

Very much indeed (3)	
Quite a lot (2)	
Not very much (1)	
Not at all (0)	

Q12 (D)
I look forward with enjoyment to things;

As much as I ever did (0)	
Rather less than I used to (1)	
Definitely less than I used to (2)	
Hardly at all (3)	

Q13 (A)
I get sudden feeling of panic;

Very often indeed (3)	
Quite often (2)	
Not very often (1)	
Not at all (0)	

Q14 (D)
I can enjoy a good book or radio or TV programme;

Often (0)	
Sometimes (1)	
Not often (2)	
Very seldom (3)	

Appendix 3

EuroQoL 5 Dimensions (EQ5D) Questionnaire (telephone script)

These questions are about your health state
Please indicate which statement best describes your own health state today

Q51
Mobility;

I have no problems walking about (1)	
I have some problems walking about (2)	
I am confined to bed (3)	

Q52
Self-care;

I have no problems with self care (1)	
I have some problems washing and dressing myself (2)	
I am unable to wash and dress myself (3)	

Q53
Usual activities (e.g. work, housework, family or leisure activities);

I have no problems with performing my usual activities (1)	
I have some problem performing my usual activities (2)	
I am unable to perform my usual activities (3)	

Q54
Pain or discomfort;

I have no pain or discomfort (1)	
I have moderate pain or discomfort(2)	
I have extreme pain or discomfort (3)	

Q55
Anxiety or depression;

I am not anxious or depressed (1)	
I am moderately anxious or depressed(2)	
I am extremely anxious or depressed (3)	

Appendix 4

Ways of Coping Questionnaire (WOCQ)

Ways of Coping
Test booklet

By
Susan Folkman Ph.D. and
Richard S Lazarus Ph.D.

Distributed by MIIND GARDEN
1690 Woodside \road Suite 202, Redwood City California 94061 (650) 261-3500

Please provide the following information:

Name_____ Date_____

Gender (circle) M F Age_____

Marital Status (tick): Single ☐ Married ☐ Widowed ☐ Separated/divorced ☐

TO THE COUNSELOR

Fill out institutional address below:

Name / Institution:

Address:

Instructions

To respond to the statements in this questionnaire, you must have a specific stressful situation in mind. Take few moments and think about the most stressful situation that you have experienced in the *past week*.

By "stressful" we mean a situation that was difficult to or troubling to you, either because you felt distressed about what happened, or because you had to use considerable effort to deal with the situation. The situation may have involved your family, your job, your friends or something else important to you. Before responding to the statements, think about the details of this stressful situation, such as where it happened, who was involved, how you acted, and why it was important to you. While you may still be involved in the situation, or it could have already happened, it should be the most stressful situation that you experienced during the week.

As you respond to each of the statements, please keep this stressful situation in mind. **Read each statement carefully and indicate, by circling 0, 1, 2 or 3, to what extent you used it in the situation**

Key: **0** = Does not apply or not used **1 =** Used somewhat
2 = Used quite a bit **3 =** Used a great deal

PLEASE TRY TO RESPOND TO EVERY QUESTION

0 = Does not apply	**1 = Used somewhat**	**2 = used quite a bit**	**3 = Used a great deal**

1	I just concentrated on what I had to do next – the next step	**0**	**1**	**2**	**3**
2	I tried to analyse the problem in order to understand it better	**0**	**1**	**2**	**3**
3	I turned to work or another activity to take my mind off things	**0**	**1**	**2**	**3**
4	I felt that time would have made a difference – the only thing was to wait	**0**	**1**	**2**	**3**
5	I bargained or compromised to get something positive from the situation	**0**	**1**	**2**	**3**
6	I did something I didn't think would work, but at least I was doing something	**0**	**1**	**2**	**3**
7	I tried to get the person responsible to change his or her mind	**0**	**1**	**2**	**3**
8	I talked to someone to find out more about the situation	**0**	**1**	**2**	**3**
9	I criticised or lectured myself	**0**	**1**	**2**	**3**
10	I tried not to burn my bridges, but leave things open somewhat	**0**	**1**	**2**	**3**
11	I hoped for a miracle	**0**	**1**	**2**	**3**
12	I went along with fate: Sometimes I just have bad luck	**0**	**1**	**2**	**3**
13	I went on as if nothing happened	**0**	**1**	**2**	**3**
14	I tried to keep my feelings to myself	**0**	**1**	**2**	**3**
15	I looked for the silver lining, so to speak: I tried to look on the bright side of things	**0**	**1**	**2**	**3**
16	I slept more than usual	**0**	**1**	**2**	**3**
17	I expressed anger to the person(s) who caused the problem	**0**	**1**	**2**	**3**
18	I accepted sympathy and understanding from someone	**0**	**1**	**2**	**3**
19	I told myself things that helped me feel better	**0**	**1**	**2**	**3**
20	I was inspired to do something creative about the problem	**0**	**1**	**2**	**3**
21	I tried to forget the whole thing	**0**	**1**	**2**	**3**
22	I got professional help	**0**	**1**	**2**	**3**

GO ON TO NEXT PAGE

0 = Does not apply	1 = Used somewhat	2 = used quite a bit	3 = Used a great deal

23	I changed or grew as a person	**0**	**1**	**2**	**3**
24	I waited to see what would happen before doing anything	**0**	**1**	**2**	**3**
25	I apologised or did something to make up	**0**	**1**	**2**	**3**
26	I made a plan of action and followed it	**0**	**1**	**2**	**3**
27	I accepted the next best thing to what I wanted	**0**	**1**	**2**	**3**
28	I let my feelings out somehow	**0**	**1**	**2**	**3**
29	I realized that I had bought the problem on myself	**0**	**1**	**2**	**3**
30	I came out of the experience better than when I went in	**0**	**1**	**2**	**3**
31	I talked to someone who could do something concrete about the problem	**0**	**1**	**2**	**3**
32	I tried to get away from it a while by taking a rest or vacation	**0**	**1**	**2**	**3**
33	I tried to make myself feel better by eating, drinking, smoking, using drugs or medications etc.	**0**	**1**	**2**	**3**
34	I took a big chance or did something very risky to solve the problem	**0**	**1**	**2**	**3**
35	I tried not to act too hastily or follow my first hunch	**0**	**1**	**2**	**3**
36	I found new faith	**0**	**1**	**2**	**3**
37	I maintained my pride and kept a stiff upper lip	**0**	**1**	**2**	**3**
38	I rediscovered what is important in life	**0**	**1**	**2**	**3**
39	I changed something so things would turn out alright	**0**	**1**	**2**	**3**
40	I generally avoided being with people	**0**	**1**	**2**	**3**
41	I didn't let it get to me: I refused to think too much about it	**0**	**1**	**2**	**3**
42	I asked advice from a relative or friend I respected	**0**	**1**	**2**	**3**
43	I kept others from knowing how bad things were	**0**	**1**	**2**	**3**
44	I made light of the situation: I refused to get too serious about it	**0**	**1**	**2**	**3**

GO ON TO NEXT PAGE

0 = Does not apply	**1 = Used somewhat**	**2 = used quite a bit**	**3 = Used a great deal**

45	I talked to someone about how I was feeling	**0**	**1**	**2**	**3**
46	I stood my ground and fought for what I wanted	**0**	**1**	**2**	**3**
47	I took it out on other people	**0**	**1**	**2**	**3**
48	I drew on my past experiences: I was in a similar situation before	**0**	**1**	**2**	**3**
49	I knew what had to be done, so I doubled my efforts to make things work	**0**	**1**	**2**	**3**
50	I refused to believe that it has happened	**0**	**1**	**2**	**3**
51	I promised myself that things would be different next time	**0**	**1**	**2**	**3**
52	I came up with a couple of different solutions to the problem	**0**	**1**	**2**	**3**
53	I accepted the situation since nothing could be done	**0**	**1**	**2**	**3**
54	I tried to keep my feeling about the problem from interfering with other things	**0**	**1**	**2**	**3**
55	I wished that I could change what happened or how I felt	**0**	**1**	**2**	**3**
56	I changed something about myself	**0**	**1**	**2**	**3**
57	I daydreamed or imagined a better time or place than the one I was in	**0**	**1**	**2**	**3**
58	I wished that the situation would go away or somehow be over with	**0**	**1**	**2**	**3**
59	I had fantasies or wishes about how things might turn out	**0**	**1**	**2**	**3**
60	I prayed	**0**	**1**	**2**	**3**
61	I prepared myself for the worst	**0**	**1**	**2**	**3**
62	I went over in my mind what I would say or do	**0**	**1**	**2**	**3**
63	I thought about how a person I admire would handle this situation and used that as a model	**0**	**1**	**2**	**3**
64	I tried to see things from the other person's point of view	**0**	**1**	**2**	**3**
65	I reminded myself how much worse things could be	**0**	**1**	**2**	**3**
66	I jogged or exercised	**0**	**1**	**2**	**3**

STOP HERE

Appendix 5

General Health Questionnaire (GHQ) – Telephone Script

GENERAL HEALTH QUESTIONNAIRE

Please read this carefully

We should like to know if you have had any medical complaints, and how your health has been in general, over the past few weeks. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past. It is important that you try to answer all the questions.
Thank you very much for your cooperation.
HAVE YOU RECENTLY:

A1	Been feeling perfectly well and in good health?	Better than usual	Same as usual	Worse than usual	Much worse than usual
A2	Been feeling in need of a good tonic?	Not at all	No more than usual	Rather more than usual	Much more than usual
A3	Been feeling run down and out of sorts?	Not at all	No more than usual	Rather more than usual	Much more than usual
A4	Felt that you are ill	Not at all	No more than usual	Rather more than usual	Much more than usual
A5	Been getting any pains in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A6	Been getting a feeling of tightness or pressure in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A7	Been having hot or cold spells?	Not at all	No more than usual	Rather more than usual	Much more than usual
B1	Lost much sleep over worry?	Not at all	No more than usual	Rather more than usual	Much more than usual
B2	Had difficulty in staying asleep once you are off?	Not at all	No more than usual	Rather more than usual	Much more than usual
B3	Felt constantly under strain	Not at all	No more than usual	Rather more than usual	Much more than usual
B4	Been getting edgy and bad tempered?	Not at all	No more than usual	Rather more than usual	Much more than usual
B5	Been getting scared or panicky for no reason	Not at all	No more than usual	Rather more than usual	Much more than usual
B6	Found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
B7	Been feeling nervous and strung up the whole time	Not at all	No more than usual	Rather more than usual	Much more than usual
C1	Been managing to keep yourself busy & occupied?	More so than usual	Same as usual	Rather less than usual	Much less than usual
C2	Been taking longer over the things you do?	Quicker than usual	Same as usual	Longer than usual	Much longer than usual
C3	Felt on the whole you were doing things well?	Better than usual	About the same	Less well than usual	Much less wee
C4	Been satisfied with the way you've carried out your task?	More satisfied	About the same as usual	Less satisfied than usual	Much less satisfied
C5	Felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less useful
C6	Felt capable of making decisions about things?	More so than usual	Same as usual	Less so than usual	Much less capable
C7	Been able to enjoy your normal day to day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual
D1	Been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
D2	Felt that life is entirely hopeless?	Not at all	No more than usual	Rather more than usual	Much more than usual
D3	Felt that life isn't worth living	Not at all	No more than usual	Rather more than usual	Much more than usual
D4	Thought about the possibility that you might make away with yourself?	Definitely not	I don't think so	Has crossed my mind	Definitely have
D5	Found at times you couldn't do anything because your nerves were too bad?	Not at all	No more than usual	Rather more than usual	Much more than usual
D6	Found yourself wishing you were dead and away from it all?	Not at all	No more than usual	Rather more than usual	Much more than usual
D7	Found that the idea of taking your own life kept coming into your mind?	Definitely not	I don't think so	Has crossed my mind	Definitely has

Appendix 6

Functional Status II – R (FSIIR)

Ask part 1 of all age relevant questions for the complete instrument. Then return and probe each item for which the response category in part 1 is marked with an asterisk (*)

It is important that part 1 of all the questions that are applicable to a child of a given age be asked first as one sequence without probing whether the response was due to illness (part 2). After asking all part 1 items, the interviewer returns to the beginning of the instrument to probe with part 2 those items receiving a starred response in part 1. The purpose of this procedure is to minimise a response set.

TELEPHONE ADMINISTRATION
Here are some statements that mothers have made to describe their children. Thinking about_____ during the last 2 weeks did he/she….

		Part 1			Part 2			
		Never or Rarely	**Some of the time**	**Almost always**	**Fully**	**Partly**	**Not at all**	
A	Eat well	0* ☐	1* ☐	2 ☐	2 ☐	1 ☐	0 ☐	FS1
B	Sleep well	0* ☐	1* ☐	2 ☐	2 ☐	1 ☐	0 ☐	FS2
C	Seem contented and cheerful	0* ☐	1* ☐	2 ☐	2 ☐	1 ☐	0 ☐	FS3
D	Act moody	0 ☐	1* ☐	2* ☐	2 ☐	1 ☐	0 ☐	FS4
E	Communicate what (he/she) wanted	0* ☐	1* ☐	2 ☐	2 ☐	1 ☐	0 ☐	FS5
F	Seem to feel sick and tired	0 ☐	1* ☐	2* ☐	2 ☐	1 ☐	0 ☐	FS6
G	Occupy him/herself	0* ☐	1* ☐	2 ☐	2 ☐	1 ☐	0 ☐	FS7
H	Seem lively and energetic	0* ☐	1* ☐	2 ☐	2 ☐	1 ☐	0 ☐	FS8
I	Seem unusually irritable or cross	0 ☐	1* ☐	2* ☐	2 ☐	1 ☐	0 ☐	FS9
J	Sleep through the night	0* ☐	1* ☐	2 ☐	2 ☐	1 ☐	0 ☐	FS10
K	Respond to your attention	0* ☐	1* ☐	2 ☐	2 ☐	1 ☐	0 ☐	FS11
L	Seem unusually difficult	0 ☐	1* ☐	2* ☐	2 ☐	1 ☐	0 ☐	FS12
M	Seem interested in what was going on around him/her	0* ☐	1* ☐	2 ☐	2 ☐	1 ☐	0 ☐	FS13
N	React to little things by crying	0 ☐	1* ☐	2* ☐	2 ☐	1 ☐	0 ☐	FS14

Appendix 7

Family Assessment device (FAD)

Family Assessment Device

Nathan B. Epstein M.D.
Lawrence M. Baldwin Ph.D.
Duane S. Bishop, M.D.

The Brown University / Rhode Island Hospital Family Research Program

Rhode Island Hospital
593 Eddy Street
Providence, RI 02903
Email: Family Research@lifespan.org

Date of Administration _____

Family Role _____

Identification Number or Family Name _____

Epstein NB, Baldwin LM, Bishop DS. The McMaster family assessment device. J Marital Family Therapy 1983; 9:171-180

INSTRUCTIONS

This booklet contains a number of statements about families. Please read each statement carefully, and decide how well it describes your own family. You should answer according to how you see your family.

For each statement there are four (4) possible responses.

Strongly Agree **(SA)**	Tick SA if you feel the statement describes your family very accurately.
Agree **(A)**	Tick A if you feel the statement describes your family for the most part.
Disagree **(D)**	Tick D if you feel the statement does not describe your family for the most part.
Strongly Disagree **(SD)**	Tick SD if you feel the statement does not describes your family at all.

These four responses will appear below each statement like this:

41. We are not satisfied with anything short of perfection

_____ SA _____ A _____D _____ DS _____

The answer spaces for statement 41 would look like this. For each statement in the booklet there is an answer space below. Do not pay attention to the blanks at the far right-hand side of each answer space. They are for office use only.

Try not to spend too much time thinking about each statement, but respond as honestly as you can. If you have trouble with one, answer with your first reaction. Please be sure to answer every statement and mark all your answers in the space below each statement.

1. Planning family activities is difficult because we misunderstand each other.

_____ SA _____ A _____D _____ DS _____

2. We resolve most everyday problems around the house.

_____ SA _____ A _____D _____ DS _____

3. When someone is upset the others know why.

_____ SA _____ A _____D _____ DS _____

4. When you ask someone to do something, you have to check that they did it.

_____ SA _____ A _____D _____ DS _____

5. If someone is in trouble, the others become too involved.

_____ SA _____ A _____D _____ DS _____

6. In times of crisis we can turn to each other for support.

_____ SA _____ A _____D _____ DS _____

7. We don't know what to do when an emergency comes up.

_____ SA _____ A _____D _____ DS _____

8. We sometimes run out of things we need.

_____ SA _____ A _____D _____ DS _____

9. We are reluctant to show our affection for each other.

_____ SA _____ A _____D _____ DS _____

10. We make sure members meet their family responsibilities.

_____ SA _____ A _____D _____ DS _____

11. We cannot talk to each other about the sadness we feel.

_____ SA _____ A _____D _____ DS _____

12. We usually act on our decisions.

_____ SA _____ A _____D _____ DS _____

13. You only get the interest of others when something is important to them.

_____ SA _____ A _____D _____ DS _____

14. You can't tell how a person is feeling from what they are saying.

_____ SA _____ A _____D _____ DS _____

15. Family tasks don't get spread around enough.

_____ SA _____ A _____D _____ DS _____

16. Individuals are accepted for what they are.

_____ SA _____ A _____D _____ DS _____

17. You can easily get away with breaking the rules.

_____ SA _____ A _____D _____ DS _____

18. People come right out and say things instead of hinting at them.

_____ SA _____ A _____D _____ DS _____

19. Some of us just don't respond emotionally.

_____ SA _____ A _____D _____ DS _____

20. We know what to do in an emergency.

_____ SA _____ A _____D _____ DS _____

21. We avoid discussing fears and concerns.

_____ SA _____ A _____D _____ DS _____

22. It is difficult to talk to each other about tender feelings.

_____ SA _____ A _____D _____ DS _____

23. We have trouble meeting our bills

_____ SA _____ A _____D _____ DS _____

24. After our family tries to solve a problem, we usually discuss whether it worked or not.

_____ SA _____ A _____D _____ DS _____

25. We are too self-centred.

_____ SA _____ A _____D _____ DS _____

26. We can express feelings to each other.

_____ SA _____ A _____D _____ DS _____

27. We have no clear expectations about toilet habits.

_____ SA _____ A _____D _____ DS _____

28. We do not show our love for each other.

_____ SA _____ A _____D _____ DS _____

29. We talk to people directly rather than through go-betweens.

_____ SA _____ A _____D _____ DS _____

30. Each of us has particular duties and responsibilities.

_____ SA _____ A _____D _____ DS _____

31. There are a lot of bad feelings in the family.

_____ SA _____ A _____D _____ DS _____

32. We have rules about hitting people.

_____ SA _____ A _____D _____ DS _____

33. We get involved with each other only when something interests us.

_____ SA _____ A _____D _____ DS _____

34. There's little time to explore personal interests.

_____ SA _____ A _____D _____ DS _____

35. We often don't say what we mean.

_____ SA _____ A _____D _____ DS _____

36. We feel accepted for what we are.

_____ SA _____ A _____D _____ DS _____

37. We show interest in each other when we can get something out of it personally.

_____ SA _____ A _____D _____ DS _____

38. We resolve most emotional upsets that come up.

_____ SA _____ A _____D _____ DS _____

39. Tenderness takes second place to other things in our family.

_____ SA _____ A _____D _____ DS _____

40. We discuss who is to do household jobs.

_____ SA _____ A _____D _____ DS _____

41. Making decisions is a big problem for our family.

_____ SA _____ A _____D _____ DS _____

42. Our family shows interest in each other only when they can get something out of it.

_____ SA _____ A _____D _____ DS _____

43. We are frank with each other.

_____ SA _____ A _____D _____ DS _____

44. We don't hold to any rules or standards.

_____ SA _____ A _____D _____ DS _____

45. If people are asked to do something, they need reminding.

_____ SA _____ A _____D _____ DS _____

46. We are able to make decisions about how to solve problems.

_____ SA _____ A _____D _____ DS _____

47. f the rules are broken, we don't know what to expect.

_____ SA _____ A _____D _____ DS _____

48. Anything goes in or family.

_____ SA _____ A _____D _____ DS _____

49. We express tenderness.

_____ SA _____ A _____D _____ DS _____

50. we confront problems involving feelings.

_____ SA _____ A _____D _____ DS _____

51. We don't get along well together.

_____ SA _____ A _____D _____ DS _____

52. We don't talk to each other when we are angry.

_____ SA _____ A _____D _____ DS _____

53. We are generally dissatisfied with the family duties assigned to us.

_____ SA _____ A _____D _____ DS _____

54. Even though we mean well, we intrude too much on others lives.

_____ SA _____ A _____D _____ DS _____

55. There are rules about dangerous situations.

_____ SA _____ A _____D _____ DS _____

56. We confide in each other.

_____ SA _____ A _____D _____ DS _____

57. We cry openly.

_____ SA _____ A _____D _____ DS _____

58. We don't have reasonable transport.

_____ SA _____ A _____D _____ DS _____

59. When we don't like what someone has done, we tell them.

_____ SA _____ A _____D _____ DS _____

60. We try to think of different ways to solve problems.

_____ SA _____ A _____D _____ DS _____

Thank you for taking the time to complete this survey.

Appendix 8

Quality of Life of Children on Home Parenteral Nutrition

Protocol Organisation Chart

Trial Coordinator (Alison Chambers) contacts participating hospitals

↓

The NNS in each centre provides contact details for all eligible families with a child on HPN

↓

Trial coordinator sends these families an information pack

↓

If the family wishes to participate they return:

- Family information sheet
- Consent form
- Assent form

↓

Within 1 week the trial coordinator (Alison Chambers) contacts the family by telephone to arrange a time for the telephone questionnaires

↓

Telephone questionnaires are administered at the agreed time. After the telephone questionnaires the family is sent 2 further postal questionnaires to complete. The main carer is asked if they can nominate a control family - if they can they are sent a written invitation to pass to said control family

↓

The case family return the postal questionnaires

↓

If the control family wishes to participate participate they return:

- Family information sheet
- Consent form
- Assent form

↓

Within 1 week the trial coordinator (Alison Chambers) contacts the control family by telephone to arrange a time for the telephone questionnaires

↓

Telephone questionnaires are administered at the agreed time. After the telephone questionnaires the family is sent 2 further postal questionnaires to complete.