Predicting Weight Loss in People with Cancer

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“Let food be thy medicine and medicine be thy food”.

Hippocrates, 460-377B.C.

ABSTRACT

Background: Malnutrition and the cachexia syndrome are common in people with cancer. A combination of reduced nutritional intake and abnormal metabolism can lead to physical and psychological disturbances which may impair quality of life and reduce survival. Improved patient outcomes are more likely if treatments and nutritional support can be initiated before significant weight loss has occurred.

Methods: A three phase, mixed methods study was undertaken. The primary aim was to gain a greater understanding of the complex factors that have an effect on, and can predict, weight loss in people with cancer. Phases I and II involved the psychometric testing of the Cancer Appetite and Symptom Questionnaire (CASQ). The instrument was tested for reliability among patients receiving radiotherapy (n=34). Predictive validity of the CASQ, using ROC curve analysis, was determined in patients with lung or upper GI cancer (n=185). Total CASQ scores (possible range, 0 to 48) were assessed at baseline, together with percentage weight change after 3 months. An exploratory qualitative study, following the principles of grounded theory, was conducted to explore the causes and influencing factors on weight change.

Results: When tested for reliability, the intra-class correlation coefficient of the CASQ was 0.80 (95% CI 0.68 to 0.92) and the difference between total CASQ scores at the two time points was -0.20 (95% CI -1.21 to 0.80). The optimum cut point of the total CASQ score to predict >5% weight loss was 31/32 (C statistic = 0.64; sensitivity 65%, specificity 62%, PPV 33%, NPV 86%), and to predict >10% weight loss was 29/30 (C statistic = 0.75; sensitivity 71%, specificity 66%, PPV 19%, NPV 95%). Exploratory modelling using multiple linear regression techniques suggested that BMI, MUST score, age and the CASQ items of enjoyment of food and pain, were most predictive of weight loss. Nine patients with lung or upper GI cancer and three carers participated in semi-structured interviews. Analysis of the data confirmed the vulnerability of this patient group in terms of symptom burden and nutritional risk. From the findings, a conceptual model that explains the influences on weight change in people with cancer was proposed.

Conclusions: Patients with lung and upper GI cancer are at high risk of malnutrition. Psychometric testing of the CASQ suggests that the instrument can predict weight loss in this patient group. Due to the low PPV, further refinements are needed before the instrument is able to be used in clinical practice. A conceptual model which explains the complex process of influences on weight change in people with cancer can improve knowledge and understanding, ultimately informing healthcare practice.

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LIST OF ABBREVIATIONS

ab-PG-SGA	Abridged Patient Generated Subjective Global Assessment
AHSP	Appetite, Hunger and Sensory Perception Questionnaire
AIDS	acquired immune deficiency syndrome
BAPEN	British Association for Parenteral and Enteral Nutrition
BCAA's	branch chain amino acids
BMI	body mass index
CASQ	Cancer Appetite and Symptom Questionnaire
CCK	cholecystokinin
CI	confidence interval
CNAQ	Council on Nutrition Appetite Questionnaire
CRP	C-Reactive Protein
CTT	classical test theory
CVI	content validity index
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0
EPA	eicosapentaenoic acid
ESPEN	European Society for Parenteral and Enteral Nutrition
FAO	Food and Agriculture Organisation of the United Nations
FAACT	Functional Assessment of Anorexia/Cachexia Therapy
GPS	Glasgow Prognostic Score
HMB	hydroxyl-beta-methylbutyrate
HR	hazard ratio
ICC	intraclass correlation coefficient
IL-1	interleukin-1
IL-6	interleukin-6
IRT	item response theory
LMF	lipid mobilising factor
MNA	Mini Nutritional Assessment
MST	Malnutrition Screening Tool
MUST	Malnutrition Universal Screening Tool
NMES	neuromuscular electrical stimulation
NICE	National Institute for Health and Clinical Excellence
NPV	negative predictive value
NRS 2002	Nutritional Risk Score 2002

NSCLC	non small cell lung cancer
NPY	neuropeptide Y
PG-SGA	Patient-Generated Subjective Global Assessment
PIF	proteolytic inducing factor
PINI	Prognostic Inflammatory and Nutritional Index
POMC	pro-opiomelanocortin
PPV	positive predictive value
REE	resting energy expenditure
ROC	Receiver Operating Characteristic
SD	standard deviation
SCLC	small cell lung cancer
S.E.	standard error
Sn	sensitivity
SNAQ	Simplified Nutritional Appetite Questionnaire
Sp	specificity
TNF- α	tumour necrosis factor-alpha
Upper GI	upper gastrointestinal
USA	United States of America
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

1.1 Introduction

Recent figures suggest that, in England, more than 250,000 people are diagnosed with cancer each year (Office for National Statistics, 2010). There are over 200 different types of cancer which together are a significant cause of death in this country. Although the incidence of cancer is increasing, promisingly over the last ten years mortality rates have fallen by around ten percent (Office for National Statistics, 2009). There are several reasons for this, such as implementation of national screening programmes and improved diagnostic techniques, as well as the advancement of cancer research resulting in better treatment options (Cancer Research UK, 2009). As people are living longer with cancer, it is inevitable that the numbers experiencing associated nutritional problems and a deterioration in nutritional status will increase. More specifically, the high incidence of the multi-dimensional metabolic syndrome of cachexia, alongside malnutrition, can lead to an increase in morbidity and mortality within this population (Lainscak *et al*., 2007). Over recent years, despite an apparent increase in research investigating weight loss and cachexia, advances in the field have been limited, and there remains no agreed treatment pathway (Braiteh *et al*., 2009; National Institutes of Health, 2010). One thing is clear, for any treatment to be effective, early identification of those at risk and timely intervention are paramount. Numerous screening instruments have been developed to identify malnutrition and a small number have been validated in people with cancer (Ottery, 1994; Thoresen *et al*., 2002; Isenring *et al*., 2006). However, no one tool encompasses all elements of the cachexia syndrome or is able to predict those people with cancer who will develop cachexia or lose weight.

The purpose of the research presented here was to develop a greater understanding of the complex processes that influence, and can predict, weight loss in people with cancer. The intention was that an increase in knowledge will enhance the nutritional management strategies in clinical practice.

This introductory chapter has three main aims. Firstly, it puts the importance of early identification of those people with cancer who are at risk of weight loss into context. Secondly, it provides information on the research conducted leading up to the Predicting Weight Loss Study which makes up the majority of the thesis. Finally,

structured around the seven chapters, an overview of the content of the thesis is given.

1.2 Background to the Predicting Weight Loss in People with Cancer study

In 2005, researchers in Nottingham began to investigate the potential use and ability of, the Council on Nutrition Appetite Questionnaire (CNAQ) (Appendix 1) to predict weight loss within the cancer population. The CNAQ was developed in the United States of America (USA) from the 29-item Appetite, Hunger and Sensory Perception Questionnaire (AHSP) (Wilson *et al*., 2005). The AHSP had previously been validated as an instrument to evaluate appetite in the healthy older population in The Netherlands. Testing had demonstrated good correlation with an alternative screening instrument, the Mini Nutritional Assessment, and with body weight (Mathey, 2001). Using the Delphi technique (Crisp *et al*., 1997) to obtain consensus opinion, content validity work by a group of experts from the Council for Nutritional Strategies in Long Term Care group developed, from the AHSP, an eight-item instrument which they called the CNAQ. The eight items of the CNAQ relate specifically to appetite and symptoms. Each item is equally scored, one to five, and a final CNAQ score is obtained by summing the eight scores. Reliability testing suggested that, when tested in the USA in a group of community dwellers and a group of residents in long term care, the CNAQ had good, and reasonable, internal consistency (Cronbach's alpha = 0.72 and 0.47 respectively). Criterion validity testing within the same two groups implied that, using a cut point of less than or equal to 28, within this population, the CNAQ scores had predictive validity in terms of five percent weight loss over six months. As the aim of the study was to validate a simple screening instrument, factor analysis was subsequently used to see if a shorter version of the CNAQ would also have predictive capabilities. Predictive validity testing showed this to be the case and four of the eight questions were put together to form the Simplified Nutritional Appetite Questionnaire (SNAQ) (Appendix 2).

1.2.1 Development of the Cancer Appetite and Symptom Questionnaire

As a screening instrument is only reliable and valid within the population that it was tested, further research would need to be undertaken for the CNAQ to be used to predict weight loss in people with cancer. Content validity testing was conducted in 2005 by members of the palliative care research team at Nottingham University Hospitals NHS Trust.

1.2.2 Content validation

The content validity of the CNAQ was established using the judgement quantification process as described by Lynn (1986). An expert panel comprised of 20 cancer service users, one caregiver and 21 oncology health care professionals was asked to rate the relevance and the succinctness of the eight items on the CNAQ. Using the scale 1 = not relevant, 2 = unable to assess without item revision, 3 = relevant but needs minor alteration and 4 = very relevant and succinct, a content validity index (CVI) was calculated as the proportion of panel members who gave a score of 3 or 4. The required minimum level of agreement was set at a CVI of greater than 0.70. Panel members were also asked to comment on the clarity of the wording and note any appetite and symptom issues that they did not feel were covered in the questionnaire. The resulting CVIs are shown in Table 1.1. All but one, item five, met the set level of agreement. In response to the comments from the expert panel, the wording of items two, four, five and six was amended. In particular, comments were made on item four which assessed taste. These related to the loss or alteration in taste experienced by patients with cancer, together with the degree to which food is enjoyed, rather than just how good or bad food tastes over all. To accommodate these comments, two new items were created to replace the original item four; 'I enjoy the food I do eat - most of the time, often, sometimes, rarely, or never'; and 'At present I have - no changes in taste, mild, moderate or severe changes in taste, or no taste at all'. An additional item was also introduced to cover the frequency of snacking. As the majority of the 23 overall comments related to a lack of inclusion of other symptoms considered likely to impact on appetite, most frequently pain and energy (fatigue), two new items were added to include these. Thus, the process resulted in the 8-item CNAQ being modified to a 12-item instrument, which was named the Cancer Appetite and Symptom Questionnaire (CASQ) (Appendix 3). The need for further reliability and validity testing of this instrument led to the research that was conducted for this doctoral degree.

Table 1.1: Content validity index (CVI) for the individual items and overall CNAQ

Item	Item theme	Frequency of comments	CVI	Changes made
1	Appetite	10	0.95	No
2	Satiety	10	0.84	Yes
3	Hunger	7	0.98	No
4	Food taste	18	0.84	Yes
5	Change in taste	19	0.57	Yes
6	Number of meals	10	0.93	Yes
7	Nausea	6	0.95	No
8	Mood	8	0.96	No
Instrument	Overall comments	23	0.88	Yes

Derived from an expert panel with 42 members, the frequency of comments and content validity index for each of the eight CNAQ items, along with the complete instrument is shown. In addition to the theme of the question, the table also indicates where changes to the wording were made.

1.3 Content of the thesis

This thesis is comprised of three studies, each contributing to the aim of predicting weight loss and understanding the experience of weight loss in people with lung and upper gastrointestinal (upper GI) cancer. Chapter 1 has introduced the thesis and provided the background research which led to the development of the three studies.

Chapter 2 reports an overview and critical appraisal of the literature within the field of malnutrition, cancer cachexia and nutritional screening. In particular, it will focus on the nutritional aspects of the condition and treatment. Current nutritional screening tools will be identified and appraised.

Chapter 3 outlines the theory underpinning the methodological approaches taken in this mixed methods, three phase study. The principles of psychometric testing of health measurement scales, specifically reliability and predictive validity testing, are discussed alongside the methods used for the Phase I and Phase II quantitative studies. The qualitative research tradition of grounded theory is presented and discussed in relation to the methods that were followed for the Phase III qualitative study. The ethical considerations of the research are also addressed in this chapter.

Chapter 4 presents the first of two quantitative phases of the study. Phase I tested the reliability of the Cancer Appetite and Symptom Questionnaire (CASQ). In this

chapter the results of such testing are described and statistically analysed. Findings are then discussed in the context of the existing literature and conclusions as to the reliability of the CASQ are drawn.

Chapter 5 describes the second quantitative study, Phase II. To determine the predictive validity of the CASQ, as a screening instrument for weight change in people with cancer, results from this longitudinal, observational study were statistically analysed. Specifically, Receiver Operating Characteristic (ROC) curves were used to determine the optimal cut points, sensitivity and specificity of the CASQ. In addition, the performance of the CASQ at predicting weight loss was compared with existing screening instruments. This chapter also contains results from exploratory modelling, using multiple linear regression techniques, to determine the optimum set of variables that could be included in a screening instrument to predict weight loss. The testing concludes with a Cox's regression survival analysis to determine the ability of the CASQ, and other measured variables, at predicting survival. This chapter ends with a discussion of the results, focusing on the use of the CASQ as a predictor of weight loss in the cancer population.

Chapter 6 reports the qualitative study which explored and analysed the experiences of people with cancer and their carers. This qualitative, Phase III study followed the principles of grounded theory and used semi-structured interviews as a data collection method. Key categories are discussed along with a substantive theory of the influences on weight change in people with cancer.

Chapter 7 brings together the discussion from all three phases of the study. Final conclusions are drawn in terms of the conceptual framework and optimum screening instrument that can be used in clinical practice to predict weight loss in people with cancer. Consideration is given to the limitations of this study as well as the implications for practice and recommendations for future research.

CHAPTER 2: LITERATURE REVIEW

Over recent years there has been a significant increase in research investigating weight loss and the cachexia syndrome in people with cancer. In addition, development of screening instruments to identify people at risk of malnutrition has been widespread. The aim of this chapter of the thesis is to provide an overview and critical appraisal of the literature within the field of malnutrition and cancer cachexia, as well as identifying and discussing the strengths and weaknesses of existing screening instruments.

2.1 Introduction

It is estimated that worldwide approximately 11 million people are diagnosed with cancer each year, with a suggested prevalence of 24.6 million (Parkin *et al*., 2005). Across the globe, incidence rates of specific cancers vary, with environmental, genetic and lifestyle factors contributing to the risk of developing the condition. In the U.K. the four most commonly diagnosed cancers, which contribute to just over half of all new diagnoses, are breast (16%), lung (13%), colorectal (13%) and prostate (12%) (Cancer Research U.K., 2009). The prognosis for patients diagnosed with these types of cancers is improving (Office for National Statistics, 2009). However, five year survival for those with lung, oesophageal and pancreatic cancer remains at less than 10% (Office for National Statistics, 2009).

Irrespective of the type of cancer, the impact on the person physically and psychologically is significant, with the range of symptoms experienced being associated with the site and stage of the disease (Reeve *et al*., 2009). In addition, the treatments provided to cure or palliate the disease frequently add to the symptom burden, increasing the risk of malnutrition and impacting considerably on quality of life (Ozturk *et al*., 2009; Saffiedine *et al*., 2009).

2.2 Incidence of malnutrition

Malnutrition has been defined as a deficiency [or excess] of macronutrients and/or micronutrients which has an adverse effect on the body's physiological, metabolic and functional capacity (NICE, 2006). There is no consensus to the specific elements, and the levels of deficiency or loss which define malnutrition (Meijers *et al*., 2009). Thus, in this thesis, the term malnutrition will be used when referring to a deficiency of nutrients, resulting in a loss of body mass.

Recent figures suggest that globally, the number of people suffering from malnutrition is estimated to be in excess of 1.02 billion (Food and Agriculture Organisation of the United Nations (FAO), 2010). By far the majority (>90%) of these people live in Africa or Asia where economic, environmental and political factors contribute to this devastating condition. People in developing countries frequently suffer from a combination of protein energy malnutrition and micronutrient deficiencies, for example, iron, vitamin A and zinc. In the more developed countries of the world, the incidence of malnutrition in the general population is lower, with the condition being more frequently associated with the presence of clinical conditions such as cancer. Within the U.K. protein energy malnutrition appears to be most predominant with specific micronutrient deficiencies being less commonly reported.

Over recent years there has been an increase in the level of research conducted to identify the incidence of malnutrition, particularly in populations that are most at risk, such as those with chronic diseases. However, due to its complexity, there is no single test to diagnose malnutrition and this has made determining its prevalence a challenge. It also means that comparison of incidence rates and trends need to be interpreted with caution. More recently the following criteria have been suggested to identify people who are at risk of the condition (NICE, 2006):

- Body mass index (BMI) less than 18.5kg/m^2.
- Percentage weight loss of greater than 10% over the previous 3 to 6 months.
- BMI less than 20kg/m^2 and percentage weight loss between 5 and 10% over previous 3 to 6 months.

To determine the extent of the problem within the U.K., for the last three years, the British Association for Parenteral and Enteral Nutrition (BAPEN) has coordinated the collection of data to establish the incidence of malnutrition in hospitals, care homes and mental health units. The most recent figures, from the screening of 5,888 people, suggest that one in three people admitted to hospital or a care home, and one in five admitted to a mental health unit, are affected by the condition (BAPEN, 2009). Research in the 1990s concluded that 40% of adults admitted into hospital were malnourished (McWhirter and Pennington, 1994). This data suggests that there has been little change in the prevalence of malnutrition over the last two decades. Acute illness is unlikely to explain this incidence alone and so it is probable that within the U.K. community, malnutrition is widespread. Analysis of the data collected by BAPEN also suggests that in addition to older age influencing nutritional status, certain clinical diagnoses are associated with a higher incidence.

For example, of those with cancer, 40% admitted to hospital and 55% admitted into care homes were malnourished (BAPEN, 2009). These figures imply that this particular disease leads to an increased risk of malnutrition, with previous studies suggesting that people with cancers of the upper GI tract are at higher risk from the condition (Segura *et al*. 2005; Read *et al*., 2006; Bozzetti, 2009). Local research in Nottingham, using the National Institute for Health and Clinical Excellence (NICE) (2006) criteria for malnutrition, also supports these findings, concluding that 58% of people, within four months of diagnosis with upper GI cancer, are malnourished (Halliday *et al*., 2009). In addition, a high prevalence of malnutrition has also been found in people with lung cancer (Kisner, 1982; Bozzetti, 2009). Locally, using the NICE criteria, 36% of people at the time of diagnosis with lung cancer have been shown to be malnourished (Chauhan *et al.*, 2007).

2.3 The cancer cachexia syndrome and malnutrition

The cachexia syndrome is important in the aetiology of malnutrition in people with cancer (Tisdale, 2002). It is also experienced by those with other conditions such as AIDS, chronic obstructive pulmonary disease and end-stage cardiac and renal failure (Von Haehling *et al*., 2009; Marks, 2009). Cachexia is a complex, multi-factorial syndrome, often defined in terms of loss of body weight. To date there is no agreed definition of the condition. Recently, in an attempt to overcome this issue, a group of experts proposed the following clinical definition of cachexia (Evans *et al*., 2008):

> "Cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity"

In conjunction with this definition, the following diagnostic criteria have been proposed (Evans *et al*., 2008):

Weight loss of at least 5% body weight in the previous 12 months, or a BMI of less than 20kg/m^2, plus three of the following:

- decreased muscle strength
- fatigue
- anorexia
- low fat-free mass index
- abnormal biochemistry (increased inflammatory markers: C-Reactive Protein or interlekin-6, anaemia: haemoglobin less than 12g/dL, or a low albumin of less than 3.2g/dL)

These criteria for diagnosis are more comprehensive than those previously used. For example, involuntary weight loss of greater than 5% in the preceding six months, with no other clinical cause, has been suggested by some clinicians (Inui, 2002), while others also require the presence of anorexia (Strasser and Bruera, 2002).

The significance of identifying patients who are in a pre-cachectic state has recently been discussed in the literature (Muscaritoli *et al*., 2009). Identification of patients at this stage may mean that interventions can be initiated earlier, helping to prevent or slow the progression of some of the devastating consequences of the cachexia syndrome. The proposed criteria for diagnosing pre-cachexia are the presence of a chronic disease accompanied by (Muscaritoli *et al*., 2009):

- weight loss of 5% or less in the previous six months
- a recurrent or chronic inflammatory state
- anorexia or anorexia related symptoms

Within the research and medical community, a consensus definition with clinically workable diagnosis criteria for pre-cachexia and cachexia, will strengthen research efforts and improve the care of patients.

Variability in the diagnosis of cachexia has impacted on prevalence studies and the capacity to establish the incidence of cachexia in the cancer population. Allowing for the absence of an agreed definition, research suggests that those people with gastrointestinal, head and neck or lung cancer are at most risk from the condition, this being due to the high prevalence of weight loss in these patient groups (Laviano *et al*., 2005). Recent work by Fox and colleagues (2009), following retrospective case note comparison using four definitions of cachexia, found that 23% of patients experienced the syndrome at some point during their cancer journey (Fox *et al*., 2009). In this particular study there was a high proportion of patients with breast, colorectal and prostate cancer included in the sample. This could therefore be an

underestimation of the cachexia incidence, particularly in the lung and upper GI cancer groups.

2.3.1 Metabolic mechanisms of cachexia

Primary cachexia is the term given to the metabolic changes that occur within the body in response to a tumour (Strasser and Bruera, 2002). The result is systemic inflammation and weight loss ensues, even in those people whose food intake remains normal (Tisdale, 2009). During uncomplicated starvation, after an initial period of adaptation, the body's response is a preservation of lean body mass, utilisation of lipid as an energy source and an overall decrease in resting energy expenditure (REE). In cachexia the response is very different as there is a prolonged increase in skeletal muscle protein catabolism and an overall decrease in protein synthesis. This is accompanied by insulin resistance and an increase in lipolysis resulting in reduced adipose stores (Tisdale, 2009). This cascade of metabolic change is similar to the body's response to trauma, injury or sepsis (Desborough, 2000). In people with cachexia REE has also been seen to be affected. Dependent on the site of the tumour, REE may be increased, decreased or remain unchanged (Tisdale, 1997). When REE is increased, whether there is an overall increase in total energy expenditure remains an area for debate. It is likely that in people, particularly with advanced disease, physical activity levels will be lower and potentially, due to a reduced food intake, energy required for diet induced thermogenesis will be less. Few research studies have been conducted to confirm this belief. Those that have use small sample sizes, no doubt in part due to the challenges involved in measuring energy expenditure in this vulnerable population. In patients with pancreatic and lung cancer, research suggests that, despite an increase in REE, total energy expenditure is not altered (Gibney *et al*., 1997; Moses *et al*., 2004). At a molecular level it has also been postulated that in patients with cancer, a shift from aerobic to less nutrient efficient anaerobic energy production in hypoxic tissue results in wastage of 'fuel', and ensuing weight loss (Tisdale, 2009).

There are several known mechanisms by which these metabolic changes of cachexia occur (Figure 2.1) (Tisdale, 2009). Pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interferon gamma are released by the host cells in response to the tumour (Argilés *et al*., 2003). These humoral factors act as mediators of inflammation, one of their roles being to initiate the release of positive acute phase proteins from the liver such as C-Reactive Protein. Circulating levels of albumin, a negative acute phase protein,

are decreased. Additionally, cytokines, specifically IL-1 and TNF-α, have been shown to induce cancer related anorexia (Argilés *et al*., 2006). It has also been demonstrated that some play a role in protein degradation in skeletal muscle through an increase in expression of the ubiquitin-proteasome proteolytic pathway (Tisdale, 2009). Furthermore, lipid metabolism is said to be influenced by the presence of IL-6 and TNF-α (Manzato and Romanato, 2006). In addition to humoral factors, it is also probable that mediators released by the tumour play a role in the observed metabolic changes. Research has shown that proteolysis-inducing factor (PIF) enhances the catabolism of skeletal muscle into constituent amino acids (Tisdale, 2009). Lipid-mobilising factor (LMF), which is also released by tumours, leads to the lipolysis of adipose tissue into free fatty acids and glycerol (Laviano *et al*., 2006). Research is ongoing to determine additional actions of humoral and tumoral mediators. It is important to consider the complexity of this area of science, the majority of our understanding is derived from in vitro studies and animal models. Whether this translates directly to humans needs further investigation.

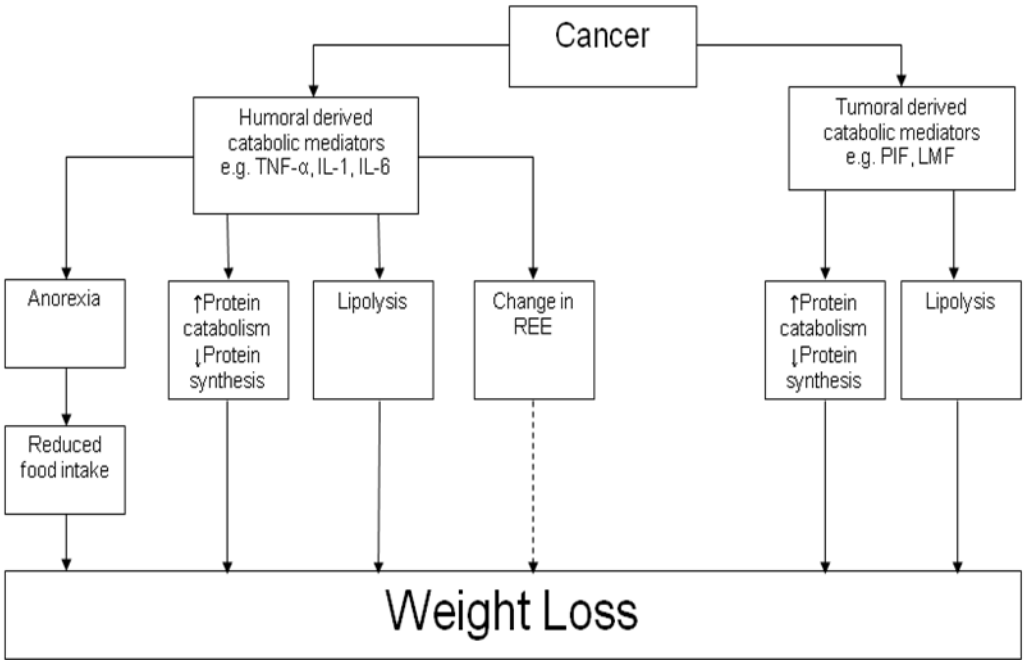

Figure 2.1: Metabolic mechanisms of cachexia contributing to weight loss (Adapted from Argilés *et al*., 2005). A solid line demonstrates where evidence exists to support the mechanism, a dotted line where the evidence is inconclusive.

2.3.2 Symptoms associated with the cachexia syndrome

Patients who have cancer experience numerous symptoms. A systematic review by Teunissen and colleagues (2007) found that in patients with incurable cancer, 37 different symptoms were described in the literature. The five most commonly reported, experienced by half of all patients, were fatigue, pain, lack of energy, weakness and anorexia. These symptoms, with the exception of pain, are commonly reported as part of the cachexia syndrome (Inui, 2002). In addition, psychological disturbances have also been associated with the syndrome. Overall, the occurrence of symptoms may be attributable to the physical presence of the tumour, including the metabolic mechanisms of cachexia, or as a side effect of surgery, chemotherapy, radiotherapy and other pharmacological management strategies. It is also clear that symptom burden, defined as the patient-reported experience of symptoms and their impact on activities of daily living and quality of life, may vary between individuals and at different stages of the disease trajectory (Davis and Kirkova, 2008).

Many studies have investigated the prevalence of single and multiple symptoms in cancer (Cooley, 2000; Teunissen *et al*., 2007; Bovio *et al*., 2009). In addition, research has demonstrated how symptoms may predict factors such as physical function and clinical outcomes (Dodd *et al*., 2001; Walsh *et al*., 2002). More recently the focus has turned to the existence of symptom clusters. Fan and colleagues (2007) defined a symptom cluster as two or more concurrently occurring related symptoms, with or without a common cause. Findings from their review of the literature showed that several studies had been conducted which investigated the symptom clusters seen within specific cancer types as well as the collective disease. Although there were some similarities between the types of clusters seen, particularly ones associated with gastrointestinal symptoms, mood and pain, it was clear that methodological difference regarding the tools used for assessment and statistical analysis meant that findings needed to be interpreted with caution. Furthermore, there is discrepancy within the literature as to the number of symptoms comprising a cluster. It is likely that further research in this area will lead to an improved understanding of symptom clusters, which in turn may help to guide treatment within clinical practice.

2.3.2.1 Anorexia

Anorexia, which can be defined as a pathologically persistent loss of the desire to eat, is intertwined with the cachexia syndrome (Wilcock, 2006). Research suggests

that the number of people with cancer experiencing anorexia is high, with more than 50% of patients with incurable disease reporting the symptom (Teunissen *et al*., 2007). The pathophysiology of anorexia is complex and not fully understood. Food intake is controlled primarily by the hypothalamus, specifically the arcuate nucleus (Figure 2.2) (Laviano *et al*., 2003). Peripheral signals regarding food intake, energy balance and adiposity status are received by the brain via the circulatory system. Within the hypothalamus these signals are transformed into neuronal responses. The metabolic and behavioural responses are then triggered through second order neuronal pathways (Laviano *et al*., 2003). Some signals such as insulin and ghrelin stimulate energy intake. Other signals such as peptide YY, leptin and cholecystokinin (CCK) inhibit energy intake. Under normal circumstances, when there is a negative energy balance, orexigenic (pro-phagic) neurones within the hypothalamus are stimulated and anorexigenic (anorexia inducing) neurones are inhibited leading to an increase in the desire to eat (Wilcock, 2006). It appears that in cachexia, cytokines directly, and indirectly via serotonin, play a role in the deregulation of the hypothalamic response, inhibiting the orexigenic neuropeptides and stimulating the anorexigenic neuropeptides (Laviano *et al*., 2003). This leads to an increase in anorexic signalling, resulting in a reduced food intake, which contributes to the decrease in body weight. Overall, research suggests that anorexia in people with cancer is associated with reduced survival (Heismayr *et al*., 2009).

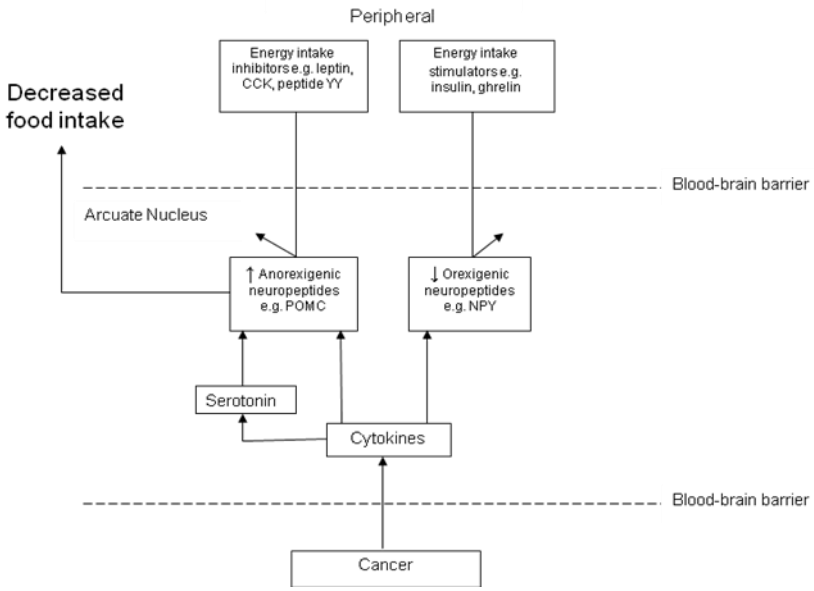

Figure 2.2: Hypothalamic regulation of appetite in cachexia (Adapted from Inui, 2002 and Laviano *et al*., 20 05). Pathways involved in the regulation of appetite in the arcuate nucleus of the hypothalamus in cachexia are shown. POMC, pro-opiomelanocortin; NPY, neuropeptide Y.

2.3.3 Psychosocial factors associated with the cachexia syndrome

In addition to the impact of the metabolic changes and symptom burden on patients with cachexia, the psychosocial aspects of the condition should not be forgotten. Indeed, more than 50% of people with advanced cancer express concern over weight loss, anorexia and eating (Hopkinson *et al*., 2006). For many people eating is a pleasurable experience and a social occasion. Research suggests that a loss of desire to eat results in meal times and eating becoming a chore (Hopkinson and Corner, 2006). In addition, embarrassment may result from uncontrolled symptoms or an inability to eat an adult portion. Studies have also shown the impact of anorexia on those caring for people with cancer (McClement *et al*., 2004). Poole and Froggatt (2002) describe the conflict between patients and family members. Keen to give advice and encouragement, carers often feel guilty at not being able to help or get frustrated with an inability to improve the person's food intake and nutritional status. Patients also express guilt at not being able to eat the food that has been prepared for them, or at being unable to help themselves to feel stronger and get better. A change in, or a loss of identity, can also be difficult for both patient and carer to adjust to. For example, a wife who has always carried out the domestic duties within the home, once diagnosed with cancer, if experiencing a loss of function and independence, may no longer be able to fulfil this role (Locher *et al*., 2009). Furthermore, in some cases concern may be related to body image. To both the patient and the family or carers, weight loss can be a constant reminder of the illness and when excessive, it is often associated with disease progression and proximity to death (Hopkinson, 2006).

2.4 Consequences of the cachexia syndrome and malnutrition

The physical effects of the cachexia syndrome manifest as malnutrition, alongside which, is a change in body composition (Fouladiun *et al*., 2005). When cachexia is present, the changes in body composition appear different to those experienced by people exposed to simple starvation, or the condition of age-related muscle wasting termed sarcopenia (Sergi *et al*., 2006). In simple starvation, lean body mass is preserved and adipose stores are used as an energy source. Put simplistically, when energy requirements exceed energy intake, weight loss ensues. This state however, can be reversed when energy intake is restored (Sergi *et al*., 2006). Age-related sarcopenia occurs in the older population and is a consequence of complex interactions of internal and external factors. An altered anabolic hormone profile, increase in oxidative stress, alongside reduced mobility and oral intake, go some way to explaining the pathophysiology (Muscaritoli *et al*., 2009). In addition, pro-

inflammatory cytokines, often associated with co-morbidities, are also likely to play a role. The resulting effect is a loss of lean body mass and associated reduction in physical function. In people with cachexia, body weight reduction occurs as a result of the metabolic factors and symptoms previously discussed. Importantly, the observed loss of lean body mass and fat mass, may be resistant to treatment (Sergi *et al*., 2006). Noteworthy at this point, is the incidence of sarcopenic obesity in the cancer population. Defined as obesity alongside depleted lean body mass, Prado and colleagues (2008) have demonstrated the increased risks for this group of people in terms of loss of function and mortality. The added threat within this population is that the signs and symptoms of the cachexia syndrome and malnutrition may be masked by obesity and, as a consequence of late detection, treatment interventions could be delayed.

Loss of lean body mass and malnutrition, whether due to the cachexia syndrome, starvation or age-related sarcopenia, have significant systemic consequences. Due to ethical issues, research into the effects of malnutrition in humans is limited, and is mainly reliant on studies carried out on conscientious objectors, individual case studies and those, often political prisoners, who choose voluntary total fasting (Altun *et al*., 2004; Kalm and Semba, 2005; Sidiropoulos, 2007). In addition, epidemiological work has added to our understanding of the macronutrient and micronutrient deficiencies seen in developing countries (Muller and Krawinkel, 2005). Specifically, in people who are malnourished, respiratory muscle weakness can result in breathlessness and difficulty expectorating. This can lead to an increased risk, or exacerbation, of a chest infection (Rochester and Esau, 1984). Compromised cardiovascular function, resulting from myocardial atrophy, can cause a reduced cardiac output, poor tissue perfusion and hypotension (Webb *et al*. 1986). Following less than a week of fasting, mucosal cell atrophy within the gastrointestinal tract can be seen (Hernandez *et al*., 1999). This can theoretically lead to an increased risk of bacterial translocation from the gastrointestinal tract, infection and sepsis. Reduced gastric and pancreatic exocrine function can also impair digestion. Furthermore, in patients with cardiac cachexia it has been suggested that impaired gastrointestinal function, due to oedema and poor perfusion, can result in fat and protein malabsorption (Celik *et al*., 2009). Malnutrition is quite clearly associated with immunodeficiency, with an increased risk of infection (Macallan, 2009) and delayed wound healing (Stechmiller, 2010). Thermoregulation is also affected by low body weight leading to an increased risk of hypothermia (Mansell *et al*., 1990). Psychologically the malnourished patient can

experience an array of symptoms including fatigue and exhaustion, deterioration in intellectual function, apathy, changes in behaviour and personality, low mood or depression (Kalm and Samba, 2005). All of these factors lead to an increase risk in terms of morbidity and mortality (Norman *et al*., 2008). More specifically, in people with cancer, conclusive evidence exists to demonstrate that those who lose weight have poorer treatment outcomes, extended hospital stays, reduced quality of life and an adverse prognosis (DeWys *et al*., 1980; Shaw-Stiffel *et al*., 1993; Andreyev *et al*., 1998; Capuano *et al*., 2008; Nourissat *et al*., 2008; Swinton *et al*., 2008). Although no conclusive data is available to determine the mechanisms by which cachexia causes death, it is likely that cardiovascular insufficiency plays a key role (Lainscak, 2009).

2.5 Management of the cachexia syndrome and malnutrition

There is no agreed management strategy for the treatment of cachexia. It is evident that to successfully treat the condition all elements; metabolic, symptomatic and psychosocial issues, will need to be addressed. Research is ongoing as to which management strategy; pharmacological, nutritional, exercise, or combination, will be most effective in alleviating the symptoms.

2.5.1 Pharmacological management

As the cachexia syndrome is multi-factorial it is unlikely that one drug will be able to combat the condition. Indeed, research into the pharmacological management focuses on the different aspects of the syndrome, resulting in four broad approaches to treatment; drugs used for the control of exacerbating symptoms, appetite stimulants, inflammatory and metabolic modulators aimed at addressing the observed metabolic changes and anabolic agents (Argilés *et al*., 2010).

To improve nutritional status, the first step should be to address and treat any symptoms which may be impacting on the patient's ability to take oral nutrition and fluids. Treatment of symptoms such as pain, constipation, nausea and vomiting are well understood and in general appropriately addressed. However, other common symptoms in people with cancer, such as early satiety, impaired taste or a sore mouth can be missed. Prokinetics, primarily metoclopramide, promote gastric emptying and, in addition to treating nausea and vomiting, can improve appetite and food intake (Von Roenn, 2002). Taste may be impaired due to the tumour, anti-cancer treatments or simply poor mouth care. Good oral hygiene is essential to prevent infections such as oral candidiasis, mouth ulcers, mucositis and a dry

mouth, all of which are common in this patient group (Brown *et al*., 2009). If present, these symptoms should be treated with a systemic antifungal such as fluconazole, topical corticosteroids, benzydamine mouthwashes and, for a dry mouth, pilocarpine and artificial saliva (Andrews *et al*. 2007). Also, there is some, albeit limited evidence to suggest that zinc deficiency may cause altered taste, and in some patients zinc supplementation may be indicated (Andrews *et al*., 2007).

Several drugs have been investigated as appetite stimulants to treat anorexia. The most frequently studied are the corticosteroids (methylprednisolone, prednisolone, and dexamethasone) and progestogens (megestrol acetate and medroxyprogesterone acetate). Although not fully understood, it is likely that the mechanisms by which corticosteroids and progestogens influence appetite is similar (Mantovani, 2006). Corticosteroids act by inhibiting prostaglandin and cytokine expression. In addition they have an anti-emetic and analgesic effect. Progestogens influence the production of pro-inflammatory cytokines and are also thought to stimulate appetite by the neuropeptide Y pathway. Although there remains no consensus as to the optimum dose or treatment duration for corticosteroids and progestogens, a systematic review of the literature concludes that they are the only drugs which have the evidence base to support their efficacy in the treatment of anorexia (Yavuzsen *et al*., 2005). Other drugs which have been investigated as appetite stimulants include the cannabinoids, in particular oral dronabinol. Research suggests that this group of drugs may have some effect on appetite, although when compared with megestrol acetate, efficacy was lower (Jatoi *et al*., 2002). Finally, studies into the effect of cyproheptadine, an antihistamine and antiserotonergic, have given conflicting results (Yavuzsen *et al*., 2005).

To manage the metabolic consequences of the cachexia syndrome, the action of several drugs has been investigated. Results between studies have been variable. As non-steroidal anti-inflammatory drugs decrease the production of prostaglandins and suppress cytokine production, theory suggests that they may have an effect on the systemic inflammatory response in the cachexia syndrome. Indeed one study has shown that ibuprofen, in combination with megestrol acetate, significantly increases weight, appetite and quality of life in people with gastric cancer (McMillan *et al*., 1999). However, the adverse gastrointestinal side effects of these drugs should be not forgotten and may even aggravate symptoms of anorexia. Thalidomide also impacts on the inflammatory response, acting to down-regulate the production of the cytokine TNF-α. Despite positive results in people with AIDS,

prospective randomised controlled trials in cancer are limited. A small study by Gordon and colleagues (2005) suggests that thalidomide may help to stabilise weight in patients with advanced pancreatic cancer. Another drug of interest which suppresses circulating TNF-α levels is melatonin. A study by Lissoni *et al*. (1996) showed that oral melatonin reduces weight loss, however, appetite and nutritional intake do not improve. Studies investigating the use of hydrazine sulphate, which inhibits hepatic gluconeogenesis and pentoxifylline, an anti-inflammatory drug, have failed to show any benefit in patients with cachexia (Loprinzi *et al*., 1994a; Loprinzi *et al*., 1994b; Goldberg *et al*., 1995). More recently, the action of insulin sensitisers (glitazones) has attracted interest. Insulin resistance is a characteristic of the cachexia syndrome and as such means that energy metabolism requires an increase in fatty acid utilisation. This in turn is less energy efficient. An incidental finding from the PROactive trial studying the use of glitazones in people with type II diabetes was a mean weight gain of 3.8kg (Dormandy *et al*, 2009). Improving insulin sensitivity in patients with cachexia may influence the anabolic effects of insulin, in addition to optimising peripheral glucose uptake and utilisation (Dohner, 2006).

The potential for anabolic agents to be used to treat anorexia and cachexia has not yet been determined as few studies have been conducted within the cancer population. Agents such as growth hormone and testosterone may maintain or improve lean body mass in people with cachexia (Mantovani, 2006). In particular, oxandrolone, a synthetic anabolic steroid, is currently being studied. Previous results from trials of the drug with patients with AIDS related cachexia were promising, showing a significant increase in weight, appetite, physical activity and strength (Berger, 1996). More recently, when used in combination with megestrol acetate, the drug has been shown to preserve lean body mass in patients receiving chemotherapy (Lesser *et al*., 2008).

The overall efficacy and safety of any pharmacological therapy needs to be determined. For drugs used to treat anorexia and cachexia, challenges in study design mean that it is often difficult to determine whether nutritional status and physical function has actually improved. More specifically, if participants are gaining lean body mass, fat mass or fluid (Von Roenn, 2006). Psychologically, patients and their carers may benefit from any type of weight gain. However, it is an increase in lean body mass, and an improved macronutrient and micronutrient intake, that is likely to improve physiological and functional capacity. Potential side-effects of the drugs must also be considered and in some cases may increase the symptom burden to an unacceptable level. It is evident that further prospective randomised

controlled trials are needed in all these areas in order to determine an optimal pharmacological strategy for the treatment of the cachexia syndrome.

2.5.2 Nutritional Support

As previously discussed, in people with cancer, there are numerous factors which contribute to a sub-optimal nutritional intake. A combination of anorexia along with systemic metabolic changes, symptom burden, anti-cancer therapies and the psychosocial aspects of the disease put patients at high risk of malnutrition. In an attempt to address the consequential increase in morbidity and mortality, U.K. national guidelines produced by NICE suggest that nutritional support should be considered in all malnourished patients (NICE, 2006). Indeed, within the cancer population it is likely that the majority of people at some stage of their illness would benefit from nutritional advice. The nature and level of the support will be dependent on many factors such as diagnosis, prognosis, function of the gastrointestinal tract, tolerance and individual wishes. Interventions should be tailored to the individual and may range from advice on food fortification, texture modification, eating patterns and oral nutritional supplements to the prescription of artificial enteral or parenteral nutrition. Remarkably, the evidence base around nutrition support and cancer cachexia is limited with no clear conclusion as to the benefits of providing nutritional interventions in this patient group. Furthermore, it has been suggested by some that the provision of artificial nutrition support may 'feed' the tumour. A recent review of the literature concludes that there is no reliable evidence upon which to base this theory (Arends *et al*., 2006). The following section will discuss how oral and artificial nutrition support can be used to treat malnutrition.

2.5.2.1 Oral nutritional support

The provision of normal food and fluids, with the required practical assistance to enable feeding, should be the first stage of providing oral nutritional support (NICE, 2006). Where nutritional requirements fail to be met, the next step should be food fortification using energy and protein dense foods and the provision of nutritious fluids (Thomas and Bishop, 2007). As the portion size eaten is likely to diminish in anorexic patients, it is also important that the frequency of eating episodes should increase. Despite its widespread application, this area of practice lacks a firm evidence base. A study by Barton and colleagues (2000) suggests that, within the hospital setting, fortification of the diet with energy, and provision of snacks, can improve overall energy intake in older patients. Conversely, with a group of malnourished nursing home residents, the same type of intervention showed an

improvement in protein, but no change to energy intake (Smoliner *et al*., 2008). Overall, in this study, functional status, as measured by physical functioning questionnaires, deteriorated. For the free living community population and those with cancer it is not clear whether fortification of the diet does improve energy, protein and micronutrient ingestion, or if it provides benefit, particularly in terms of physical function and quality of life.

Within the U.K., dietitians possess the necessary skills to provide individualised dietary counselling to people regarding food fortification. Recent studies in patients with cancer investigating the efficacy of dietary counselling are limited, and confined to those patients undergoing radiotherapy treatment. In patients with colorectal cancer receiving radiotherapy, research suggests that this type of counselling can improve energy and protein intake (Ravasco *et al*., 2005). In this study, quality of life, when measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC QLQ-C30) (Appendix 4) , also improved. Furthermore, three months after completion of the radiotherapy the benefits remained. The findings from a recent study by Weekes and colleagues (2009), in a patient population with chronic obstructive pulmonary disease, concur. The results suggest that dietary counselling and food fortification lead to an increased energy and protein intake when compared with simple provision of a dietary information leaflet. This improvement in intake corresponded to an increased weight and improved quality of life score. There was however, no observed increase in objective functional measures such as muscle strength and respiratory function. In contrast, in a study of patients receiving chemotherapy for lung, breast or ovarian cancer, only a non significant increase in weight was detected in the group receiving dietary counselling (Ovesen *et al.,* 1993). Although in the same group there was a statistically significant increase in triceps skinfold thickness, the conclusion of the authors was that there was no clinical benefit of providing dietary counselling in this patient group.

For some people, regardless of being counselled on ways to maximise their macronutrient and micronutrient intake, the desired increase in food ingestion is not achievable. At this point the provision of prescribed propriety oral nutritional supplements should be considered (NICE, 2006). An extensive range of nutritionally complete oral sip feeds exist. The majority are milk-based sweet drinks although juice-style and soups are also available. In addition, powder carbohydrate, fat and protein modulars, which can be added into foods and fluids, can be prescribed.

Previous evidence suggests that in a malnourished population, when compared with routine clinical care, oral nutritional supplement drinks can reduce complications and mortality rates (Stratton, 2000). More recently, in adults with illness-related malnutrition, a review of the literature investigating the benefit of oral nutritional supplements compared with the use of dietary advice showed that nutritional interventions can improve anthropometric measures (Baldwin and Weekes, 2008). However, findings from the review did not allow for a conclusion to be made in terms of which intervention was most effective. Two other systematic reviews which investigated the use of nutritional supplements have recently been conducted. Milne and colleagues (2009) conclude that in older people who are at risk of malnutrition the use of nutritional supplements can lead to a small but consistent increase in weight. In contrast, in patients with stable COPD, a review of 14 studies suggests that there was no significant effect of nutrition supplementation in terms of improved anthropometrics, physical or lung function (Ferreira *et al*., 2005). Overall, none of the reviews found a significant decrease in mortality in those taking nutritional supplements. Despite these inconclusive findings, and the small number of studies specifically investigating the cancer population, recent guidelines produced by the European Society for Parenteral and Enteral Nutrition (ESPEN) propose that in patients with cancer receiving radiotherapy, or radio-chemotherapy, there is sufficient evidence to support the use of oral nutritional supplements (Arends *et al*., 2006). For those patients receiving radiotherapy, this conclusion is based on the findings from four small studies, all but one being conducted pre 2000, with a combined sample of predominantly patients with head and neck cancer, and from a recent meta-analysis (Thiel *et al*., 1988; Arnold *et al*., 1989; Nayel *et al*., 1992; Isenring *et al*., 2004; Elia *et al*., 2006). More specifically, the meta-analysis established that the use of oral nutritional supplements can significantly increase energy intake by 381kcal/day (95%CI 193 to 569) (Elia *et al*., 2006). However, this finding should be interpreted with caution as it was calculated using the results of only three studies, all conducted in the 1980s, and one of which used elemental supplements as treatment. For patients undergoing chemotherapy it is apparent that the ESPEN recommendations for the use of oral nutritional support are based on expert opinion, rather than on randomised controlled trials. As the reviewed studies involved mainly patients with head and neck cancer receiving radiotherapy, it is not appropriate for inferences to be made about a population of patients receiving chemotherapy, particularly when that treatment is likely to have a palliative intent. The main reason for this is the differences between the patient groups. For those

who have incurable cancer, outcomes will differ as a consequence of disease and symptom progression, thus masking the true effects of the trialled intervention.

It is likely that dietary counselling and oral nutritional supplements can be beneficial to malnourished patients with cancer. Larger randomised controlled trials are needed to determine their efficacy and long term benefits. In addition, studies need to focus on the inclusion of patients with a range of cancer diagnoses, stages of disease and treatment plans. The use of modular products as well as the sip feeds which have traditionally been included in research should also be investigated. Furthermore, patient compliance with prescribed supplements has been identified as an issue and must be addressed if the benefits are to be optimised (Bruce *et al*., 2003). Overall, careful consideration needs to be given to the outcome measures chosen to determine the efficacy of the nutritional intervention, and these may differ dependent on the population being studied and the stage of their disease.

2.5.2.2 Nutraceuticals

In addition to food fortification advice, and the use of nutritionally complete supplement drinks, the potential benefit of other nutrients has been investigated. The term ‘nutraceuticals’ arises from nutrients being used as pharmaceutical agents in an attempt to influence the metabolic pathways of the cachexia syndrome (Dahele, 2006). Eicosapentaenoic acid (EPA) is a n-3 fatty acid. Research suggests that EPA impairs the action of proteolytic inducing factor (PIF) and also down-regulates the cytokine induced systemic inflammatory response (Barber *et al*., 2005). In people with pancreatic cancer, at a dose of 6g a day, EPA capsules have been shown to stabilise weight (Barber *et al*., 2001). In contrast to these results, when used in a population of patients with advanced cancer, EPA had no significant effect on any of the measured parameters (Bruera *et al*., 2003). Despite the uncertainty within the evidence base, oral nutritional supplement drinks containing EPA, for example, Prosure (Abbott Nutrition), are available and can be prescribed for people with cancer. To date, published data on their efficacy is confined to those with pancreatic cancer. In a randomised control trial conducted by Fearon and colleagues (2003), despite poor compliance, there was a significant increase in energy intake in those receiving EPA compared with those having a standard supplement. Further research is required to establish their usefulness within other cancer groups.

Synthesis of muscle protein is reliant on an optimal supply of amino acids. In people with cachexia circulating serum levels of amino acids, including branch chain amino acids (BCAA's), have been shown to be reduced (Norton *et al*., 1985). The BCAA's, particularly leucine, and to a lesser extent isoleucine and valine, are not only important for protein synthesis, they are also a key component in the signalling pathways which initiate muscle protein synthesis (Nakashima *et al*., 2005). Recent research using cachectic-tumour induced mice as a model has shown that leucine and valine increase protein synthesis and decrease protein catabolism resulting in significant suppression of weight loss (Eley *et al*., 2007).

Increased serotonergic activity in the brain results in a decrease in the desire to eat (Davis *et al*., 2004). Tryptophan, a BCAA, is a precursor to serotonin and therefore has a role to play in the pathogenesis of anorexia. Research suggests that in response to a tumour, circulating concentrations of tryptophan are increased. This results in tryptophan competing with other BCAA's to cross the blood brain barrier, higher levels of serotonin in the brain and ultimately an increase in anorexia (Cangiano *et al*., 1990). Oral supplementation of competing BCAA's (leucine, isoleucine and valine) in a small group of people with cancer has been shown to significantly reduce anorexia and increase food intake (Cangiano *et al*., 1996).

The effect of other amino acids on the cachexia syndrome has also been investigated. Glutamine, arginine and hydroxy-beta-methylbutyrate (HMB) which is a precursor of leucine, have been shown to positively influence protein turnover. In a study by May and colleagues (2002) patients with advanced cancer given a supplement of glutamine, arginine and HMB showed an increase in fat free mass. The exact mechanism for this is not yet understood and further research is required. In addition, both glutamine and arginine have been shown to influence the immune system, and supplementation of arginine to improve wound healing (Lind, 2004; Medina, 2001).

2.5.2.3 Artificial nutritional support

When macronutrient and micronutrient requirements are unable to be met orally, consideration needs to be given to the use of artificial nutrition support (NICE, 2006). There are two types of artificial nutrition support; enteral and parenteral. Enteral nutrition involves the placement of a feeding tube into the stomach or small bowel, usually via the nasal cavity or directly through a stoma. A nutritionally complete liquid feed is then delivered into the gastrointestinal tract. Parenteral

nutrition is the provision of nutrients intravenously via a central or peripherally inserted catheter. When the gastrointestinal tract is functioning, enteral feeding is regarded as the route of choice (NICE, 2006). However, both forms of nutrition support carry some element of risk, such as the possibility of infection or metabolic disturbances (Cataldi-Belcher *et al*., 1983; Gomez *et al*., 2008). Some authors argue that the increased risks associated with parenteral nutrition may have been exaggerated with a previous review of the literature suggesting that it is as effective and as safe as the enteral route (Jeejeebhoy, 2001). In addition, others have found parenteral nutrition to be better tolerated by patients (Bozzetti *et al*., 2001). However, a more recent meta-analysis concluded that in patients with cancer having surgery, post-operative enteral tube feeding resulted in a shorter hospital stay (1.7 days 95%CI 0.9 to 2.5) and fewer complications (OR 0.62 95%CI 0.50 to 0.77) compared with parenteral nutrition (Elia *et al*., 2006).

In people with cancer, based on a review of the literature, the recommendation is that enteral nutrition should be commenced when food intake is, or is likely to be, less than 60% of requirements for more than 10 days (Arends *et al*., 2006). The same guidelines also state that for patients receiving palliative care, providing they are not in the terminal phase of the disease trajectory and that they are in agreement, enteral nutrition should be provided to minimise weight loss. There is some evidence to suggest that the use of enteral nutrition in patients with head and neck or gastrointestinal cancer can stabilise weight (Raykher *et al*., 2008; Sironi *et al*., 2008). However, there is little evidence to show that body composition or functional status is improved.

Recently, guidelines regarding the use of parenteral nutrition in people with cancer, based on a review of the literature, have been published. In patients with cancer who have a prognosis of more than two to three months, and whose gastrointestinal tract is not accessible or is not functioning, parenteral nutrition should be considered (NICE, 2006; Bozzetti *et al*., 2009). It appears that there is evidence to support the use of this type of intervention in patients who are unable to be fed enterally. However, conclusions on the clinical benefits should be made tentatively. A very small study (n=3) of patients with gastric disease showed that compared with before parenteral nutrition was initiated, intravenous feeding resulted in a statistically significant increase in protein synthesis, although protein turnover remained constant (Bozzetti *et al*., 2000). Another study suggests that in patients receiving supportive palliative care, weight and quality of life indices remained stable until

death (Bozzetti *et al*., 2002). It is not clear if the observed weight gain in this study was due to an increase in body water, fat or lean mass. In addition, there are still questions as to whether this type of therapy results in an improvement in functional status. However, in a population where deterioration in nutritional status is almost inevitable, maintenance of nutritional and quality of life parameters are likely to be appropriate outcomes.

Across Europe there appears to be a vast difference in the provision of parenteral nutrition in the cancer population. In 1997 ESPEN conducted a survey investigating the number of people from seven E.U. countries who were on home parenteral nutrition (Van Gossum *et al*., 1999). At this time it was clear that the picture in the U.K. was very different to that seen in other countries. Only five percent of patients in the U.K on home parenteral nutrition had a primary diagnosis of cancer. This was much less than in other countries such as The Netherlands where the numbers of patients receiving this type of nutrition therapy who had cancer was 60%. The survey also suggested that in Germany and Sweden the prevalence was likely to be even higher, at 70% and 80% respectively, although overall reporting in these countries was said to be below the optimum (Van Gossum *et al*., 1999). Ten years later, the picture does not appear to have changed. Data from 2008 suggests that the point prevalence of people receiving home parenteral nutrition in the U.K. was $6.7/10^6$ (British Artificial Nutrition Survey, 2009). Only six percent of these patients had a diagnosis of cancer. Results from a recent study in Italy showed that point prevalence of home parenteral nutrition was $31.7/10^6$, with 61% having cancer (Pironi *et al*., 2007). Furthermore, in contrast to the U.K., there appears to be a significant number of patients in Italy receiving both parenteral and enteral nutrition simultaneously. This is a practice reflected in other countries where patients are receiving home parenteral nutrition alongside oral diet and nutritional supplements (Orrevall *et al*., 2009). The reasons behind this disparity in practice are not fully understood, although they are likely to be related to differences in culture and attitudes of healthcare staff, as well as the economic pressures around funding of this intervention (Orrevall *et al*., 2009).

2.5.3 Exercise

Skeletal muscle atrophy in patients with cancer may occur as a consequence of the cachexia syndrome. The likely cause is a combination of metabolic processes, exacerbated by inactivity, resulting in reduced protein synthesis and increased protein degradation (Tisdale, 2009). Contractile activity may help in part to attenuate

muscle loss by suppressing the local inflammatory response and enhancing insulin sensitivity (Ardies, 2002). Exercise has been shown to have a protective effect against the loss of muscle fibre by inhibiting the pathways used to cause muscle atrophy (Sandri *et al*., 2006). Research suggests that a therapeutic exercise programme can help to promote physical, as well as psychological well being in people with cancer (Oldervoll *et al*., 2004; Oldervoll *et al*., 2006; Velthuis *et al*., 2010). Within the literature the majority of studies, using both home-based and aerobic exercise programmes, appear to have been done with patients who have non metastatic breast or prostate cancer (Velthuis *et al*., 2010). There remains a lack of research looking at therapeutic exercise in people with incurable lung, upper GI, and advanced cancer, particularly, those with a poorer performance status. This may, in part, be due to the symptom burden experienced by this group, and difficulty in adherence to activity programmes.

An alternative to physical activity programmes in people with cancer is neuromuscular electrical stimulation (NMES). In people with chronic obstructive pulmonary disease NMES has shown positive results in improving muscle strength, endurance and quality of life (Neder *et al*., 2002). Research is ongoing into the effect of NMES in people with lung cancer (Maddocks *et al*., 2006).

2.5.4 Supportive care

As discussed earlier, the psychosocial aspects of malnutrition and cachexia are important to consider. Supportive care, in this instance, is the term used to help people with cancer, their families and caregivers cope with the symptoms of the cachexia syndrome. Hopkinson (2007) suggests how supportive care should be managed, highlighting the need for assessment of the situation, acknowledgement and normalisation of the problem, provision of information and ongoing support in managing conflict and change or loss of identity. Rosenbaum and colleagues (2004) share this view and report how a cancer supportive care programme improved the satisfaction and quality of life of patients in their locality. In particular, participants reported an improved sense of wellbeing, increase in energy and feelings of empowerment. Noteworthy is the sometimes controversial use of complementary and alternative medicine in cancer care. There is evidence to suggest that for some people, use of this type of therapy may improve physical and psychological symptom burden, (Jacobsen *et al*., 2000) with reflexology and aromatherapy being some of the most commonly used treatments (Gage *et al*., 2009). However, a

review by the NICE suggests that overall, conventional evidence to their benefit is lacking (NICE, 2004).

2.6 Screening for malnutrition and cachexia

Whatever the management strategy of choice for malnutrition and cachexia, early identification of people at risk and timely intervention is vital. Although there are screening tools that individually screen for malnutrition, adverse symptoms and systemic inflammation, to date there is no one simple and practical tool that encompasses all aspects of the cachexia syndrome. The subsequent sections will focus on the screening instruments which are most frequently discussed in the literature, in relation to the cancer population.

2.6.1 Screening for malnutrition

Within the literature there appears to be some confusion as to the definition of nutritional screening and nutritional assessment. To clarify, screening and assessment as defined by the British Dietetic Association (1999) are as follows:

> "Nutritional screening is a simple and rapid process of identifying clinical characteristics known to be associated with malnutrition. The screening process is intended to identify individuals who are at risk of becoming malnourished and who require referral to a state registered dietitian for a comprehensive nutritional assessment".

> "Nutritional assessment is a comprehensive process of identifying and evaluating the nutritional status of an individual using appropriate, measurable methods. It consists of gathering data using four main techniques: history taking, nutritional anthropometry, physical examination and biochemical tests. Nutritional assessment is able to quantify impairment of nutritional status".

Within the U.K, in an attempt to combat the absence of awareness of malnutrition in both the hospital and community settings, recommendations on screening practices were made by The National Institute for Health and Clinical Excellence. The guidelines state that all patients admitted to hospital should be screened for risk of malnutrition, at admission and weekly thereafter (NICE, 2006). In addition, out-patients should be screened at their first appointment, as should new registrants at G.P. practices. Finally, all people entering a care home should be screened on admission and, as in all other settings, when there is clinical concern. The guidelines suggest that the screening process should involve measurement of body

mass index and percentage unintentional weight loss over time, plus whether there has been, or is likely to be, a reduced food intake. The Malnutrition Universal Screening Tool (MUST) (Appendix 5) is given as an example of an instrument that could be used.

As will be discussed in Chapter 3, development of any screening instrument is a complex and lengthy process. The ultimate aim of a tool is for it to be successfully implemented into clinical practice. For this to happen, it should be quick and easy to use, and have proven reliability and validity. Over the last two decades numerous screening instruments have been developed to identify people at risk of malnutrition. A review of the literature by Green and Watson (2005) found published information on 71 different screening/assessment instruments for malnutrition. Most of the 35 reviewed instruments incorporated anthropometric measurements such as weight change. In view of the difficulties involved in weighing some patients, other instruments used a subjective assessment of body weight or mid upper-arm anthropometry as an indicator of muscle mass. Factors associated with nutritional intake and nutritional requirements, such as presence of disease or symptoms were also included in other tools. Most instruments used a scoring system to identify those at risk of malnutrition although some relied on a subjective assessment of risk. Since an agreed definition and gold-standard test for malnutrition do not exist, consensus on the most appropriate instrument, and if it is indeed identifying those at risk of malnutrition, is limited (Green and Watson, 2005; Meijers et a., 2009). The ambiguity around the condition also makes it difficult to compare the outcomes from previous research studies where definitions may differ. Furthermore, the use of diverse methodologies and limited statistical analysis included in some papers hinder the process further (Green and Watson, 2005).

To date, only a handful of tools have been validated for use specifically with people who have cancer. As studies are limited, and due to the heterogeneity of the cancer diagnosis, these instruments should be viewed and used with caution until more thorough testing within a range of tumour types is conducted. A universal consensus definition amongst experts as to what constitutes malnutrition will benefit this area of research.

2.6.1.1 Subjective Global Assessment

Subjective global assessment (SGA) (Appendix 6) was first validated as a screening tool to detect malnutrition in 1987, with the original study investigating its use in

patients undergoing gastrointestinal surgery (Detsky *et al*. 1987). The SGA is designed to be completed by the health care professional. Five questions relating to change in weight, change in food intake, gastrointestinal symptoms, functional capacity and disease-related metabolic stress are followed by a physical examination to determine muscle and adipose status and fluid balance. Patients are subjectively categorised as well nourished, moderately malnourished or severely malnourished. More recently the SGA has undergone validity testing in an in-patient palliative care setting (Thoresen *et al*., 2002). Comparing the results of the SGA to objective anthropometric and serum protein measurements to identify malnutrition, the sensitivity and specificity of the SGA was 96% and 83% respectively. However, consideration must be given to the small sample size (n=46), the high incidence rate of malnutrition (61%) and the fact that only one observer was used. The predictive validity of the SGA has also been investigated in people with advanced colorectal and ovarian cancer (Gupta *et al*., 2004; Gupta *et al*., 2008). In both groups there was a significantly shorter prognosis for patients who were identified as being severely malnourished by SGA compared with those classified as well nourished.

2.6.1.2 Patient Generated Subjective Global Assessment

In order to improve the sensitivity of the SGA, particularly in measuring changes in nutritional status over short periods of time, the tool was adapted to form the patient generated subjective global assessment (PG-SGA) (Appendix 7) (Ottery, 1994). This modification was made, in part, to improve the use of the tool within the oncology setting. The content of the PG-SGA is similar to the SGA, including questions about recent weight change, food intake, symptoms, activity and function which are self-completed by the patient. The physical assessment, subjective classification of the degree of risk and scoring are then completed by a health care professional. The PG-SGA has been shown to have demonstrated validity and inter-rater reproducibility when used with in-patients with cancer, oncology patients receiving radiotherapy and medical oncology patients attending a day unit (Bauer *et al*., 2002; Isenring *et al*., 2003; Read *et al*., 2005). The need to perform a physical examination in order to complete both the SGA and the PG-SGA can be time consuming, and this, coupled with the need to be trained in its use, has meant that implementation of either tool within clinical settings in the U.K. has been limited.

A recent study by Stoyanoff and colleagues (2009) tested an abridged version of the PG-SGA (ab-PG-SGA) (Appendix 8). The results suggest that this shorter, less complex screening instrument, when tested in an oncology out-patient setting with

patients undergoing chemotherapy, has a comparable sensitivity and specificity to the PG-SGA. Although further testing in other cancer groups is necessary, these findings may influence use of the ab-PG-SGA within U.K. oncology out-patient clinics.

2.6.1.3 Malnutrition Screening Tool

The malnutrition screening tool (MST) (Appendix 9) was developed in Australia and has been validated against the SGA in patients with cancer receiving radiotherapy and against the PG-SGA in people being treated with chemotherapy (Ferguson *et al*., 1999; Isenring *et al*., 2006). Unlike the SGA and PG-SGA the MST is simple and quick to complete, although it provides little information in terms of food intake, symptoms and function. The MST takes a three step scored approach. Patients are asked if they have recently unintentionally lost weight, if so, how much and if they have a reduced food intake due to a decrease in appetite. A score of two or more, derived from a weight loss of greater than six kilograms, or less than five kilograms with a decreased appetite, classifies the patient at risk of malnutrition. Although the sample size across the two completed studies was relatively small (n=156), the MST was shown to have good inter-rater reliability, 100% sensitivity and a specificity of 81% and 92% respectively (Ferguson *et al*., 1999; Isenring *et al*., 2006). More recently, lower levels of sensitivity (81%) and specificity (72%) were found by Stoyanoff and colleagues (2009) when they compared the use of the MST to the ab-PG-SGA in a group of oncology patients who were receiving chemotherapy. The authors concluded that the ab-PG-SGA should be the instrument of choice in the oncology out-patient setting.

2.6.1.4 Malnutrition Universal Screening Tool

The Malnutrition Universal Screening Tool (MUST) (Appendix 5) was developed in 2003 by the Malnutrition Advisory Group, a standing committee of BAPEN (Elia, 2003). Although not specifically tested in the cancer population, the MUST was validated against various other screening tools such as the SGA, Mini Nutritional Assessment (MNA) and MST (Stratton *et al*., 2004). It is validated for use in both acute and community settings and has proven reliability, face validity, content and concurrent validity (Elia, 2003). In the acute hospital setting, research suggests that in the elderly population, MUST also has predictive validity for length of stay, discharge destination and mortality (Stratton *et al*., 2006). Calculation of the MUST score is relatively simple and quick, with research suggesting that it takes between three and five minutes to complete (Stratton *et al*., 2004). Identification of patients at

risk of malnutrition using the MUST involves five steps. The first step is the calculation of body mass index (BMI). A BMI below 18.5kg/m^2 results in a score of two being awarded, between 18.5 kg/m^2 and 20 kg/m^2 a score of one and above 20 kg/m^2 a score of zero. The second step is the calculation of percentage unintentional weight loss over the previous three to six months. Greater than 10% weight loss scores two, between 5% and 10% scores one and where weight loss is less than 5% a score of zero is awarded. Determination of whether disease state has resulted in, or is likely to result in, no nutritional intake for more than five days is the third step, and where this is likely, a score of two is given. The fourth step involves adding up the scores. A score of two or more indicates that the patient is at high risk of malnutrition, a score of one, medium risk and zero, low risk. The final step is the action which is taken as a result of the screening process. This is dependent on the severity of the risk and local policy but may, for example, include a referral to the dietetic service for those deemed at high risk.

Although good to excellent agreement was found between the MUST and SGA (k = 0.78), and the MUST and MST (k = 0.71) in groups of medical in-patients, when tested with in-patients at an oncology hospital, the sensitivity and specificity of the MUST was found to be low. This led to the conclusion that it should not be used in hospitalised people with cancer (Bauer and Capra, 2003). The findings from research by Roulston and McDermott (2008) appear to concur with this conclusion. However, this study was conducted retrospectively using the case notes of 52 patients accessing an oncology service. As only an abstract has been published, no information is available regarding the diagnoses of patients or what constituted the dietetic objective assessment. Further research investigating the use of the MUST is needed to clarify whether indeed the instrument is reliable and valid within the cancer population.

2.6.1.5 The Mini Nutritional Assessment

The Mini Nutritional Assessment (MNA) (Appendix 10) was initially developed and validated to screen for malnutrition in the older population. It consists of six scored questions relating to weight loss, BMI, acute physical and mental disease state and mobility. Validity testing demonstrated that the tool had a high sensitivity and specificity of 96% and 98% respectively when tested in an older age group (Vellas *et al*., 1999). More recently, use of the tool has been investigated in people with cancer (Slaviero *et al*., 2003; Read *et al*., 2005; Gioulbasanis *et al*., 2008; Roulston and McDermott, 2008). In a group of patients with advanced cancer receiving

chemotherapy Slaviero and colleagues (2003) demonstrated that the MNA was correlated with C-Reactive Protein serum concentration and baseline weight loss. It has also been claimed that the MNA can be used to identify early cachexia in patients with lung cancer (Gioulbasanis *et al*., 2008). In this study, those identified as malnourished or at risk by the MNA were shown to have reduced mortality. The authors also demonstrated a relationship between results of the MNA and biochemical markers of cachexia such as C-Reactive Protein, albumin, interleukin-6 and interleukin-8. Results of a small study suggest that the MNA is comparable to the MST at identifying patients at risk of malnutrition in the oncology setting (Roulston and McDermott, 2008). However, in a group of newly diagnosed patients with cancer, when compared with the PG-SGA, the MNA has been shown to lack specificity (Read *et al*., 2005).

2.6.1.6 The Nutrition Risk Screening 2002

A final screening instrument which is noteworthy is the Nutrition Risk Screening 2002 (NRS 2002) (Appendix 11). This two step screening approach has been endorsed by ESPEN for use in the hospital setting (Kondrup *et al*., 2003a). Similar in content to the MUST, the NRS 2002 uses a two stage approach to identify patients as no, low, medium or high risk of malnutrition. The second stage requires a percentage quantification of food intake compared with normal requirements as well as considering the impact of disease on requirements. The methodology used to validate this instrument involved the application of the screening instrument to retrospective analysis of randomised controlled trials which had been conducted to investigate the benefits of nutrition support on outcome (Kondrup *et al*., 2003b). Details regarding prospective psychometric testing were not found in the literature. As it is likely that this instrument would be completed predominantly by nursing staff, the need to determine what percentage of nutritional requirements are being met by current food intake may prove difficult in routine clinical practice. However, that along with the potential impact of disease status on nutritional requirements, are important factors to consider when determining risk from malnutrition.

2.6.2 Screening for the metabolic changes of cachexia

As with malnutrition, there is no agreed gold standard test to screen or diagnose a person with cachexia. Research has been conducted to investigate the use of biochemical markers as screening or assessment parameters to identify patients at risk from the condition, with the focus predominantly on the use of serum proteins such as albumin, or the inflammatory marker, C-Reactive Protein. Serum

concentrations of albumin decrease during times of metabolic stress, infection and inflammation. Albumin is also affected by hydration status and has a long half-life making its use as an indicator of nutritional status questionable (Chojnowska, 1996). Pre-albumin may be of greater use as it has a much shorter turnover time and has been shown to have prognostic capabilities when measured in a group of patients with cancer receiving parenteral nutrition (Bourry *et al*., 1982). Overall, there appears to be a lack of research into the use of pre-albumin as a marker of nutritional status, particularly in people with cancer.

During times of metabolic stress, inflammation and infection the release of C-Reactive Protein from the liver is mediated by cytokine activity, in particular interleukin-6 (Heinrich *et al*., 1990). C-Reactive Protein serum concentrations appear elevated in people with cancer and, in addition, have been shown to be a prognostic indicator of survival in people with advanced disease (Nelson and Walsh, 2002; Walsh *et al*., 2003). Raised interleukin-6 levels have also been associated with increased weight loss in people with lung, pancreatic and advanced cancer (Falconer, 1994; Scott, 1996; Walsh *et al*., 2003). Two prognostic scoring systems have been developed and validated in people with cancer. The simplest is the Glasgow Prognostic Score (GPS) (Appendix 12) which involves the measurement of serum albumin and C-Reactive Protein levels. Serum albumin concentrations less than 35g/l and C-Reactive Protein levels greater than 10mg/l score one point. An overall score of one or two is classed as abnormal, and in people with lung and upper GI cancer, this has been correlated with a reduced performance status and survival (Brown *et al*., 2006). However, the study also showed that raised levels of C-Reactive Protein alone showed similar correlations, questioning the need to measure albumin and calculate the GPS.

The other scoring system is the Prognostic Inflammatory and Nutritional Index (PINI) (Appendix 13) which was originally developed and validated as a predictor of morbidity and mortality in patients with burns (Kudlackova *et al*., 1990). The PINI measures serum levels of C-Reactive Protein, alpha-1-acid glycoprotein which is another positive acute phase protein against albumin and pre-albumin. In 50 in-patients, at a palliative care unit, the PINI scores were significantly higher in those with advanced cancer, anorexia and weight loss (Nelson and Walsh, 2002). However, the authors of this study also suggested that C-Reactive Protein alone is a useful predictive nutritional indicator.

2.6.3 Screening for symptoms of cachexia

Of the nutritional screening tools previously discussed, there is no consistent approach to determining what symptoms may be impacting on the nutritional status of the patient. A recent systematic review of the literature found 21 cancer symptom assessment instruments which the authors judged appropriate for use within the clinical setting, the majority of which had been developed to assess the physical and psychological symptoms of a general cancer population (Kirkova *et al*., 2006). The methodological quality of the studies varied, as did the estimated reliability and validity of the instruments and, in the opinion of the authors, none met all the criteria for an ideal assessment tool. Furthermore, there was often no attempt to assess symptom severity and level of distress which are important factors when determining overall burden. Finally, all instruments appeared to have been designed for assessment of symptoms rather than for screening purposes *per se*.

Several instruments have been developed to measure overall quality of life. For example, the EORTC QLQ-C30 (Appendix 4) which involves patients rating their symptom severity on a four point scale (Aaronson *et al*., 1993). Another, the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) (Appendix 14) appetite scale was designed to measure the impact of appetite and the cachexia syndrome on quality of life (Chang *et al*. 2005). Both of these instruments have some proven predictive ability in terms of survival (Chang *et al*., 2005; Grande *et al*., 2009). However, neither were designed for the purpose of screening. Their main use being as a research instrument or, for example, as a tool to monitor changes in self-reported quality of life following the instigation of a new therapy.

One appetite and symptom screening instrument that has been validated for use within the general population in the United States of America is the Council of Nutrition Appetite Questionnaire (CNAQ) (Appendix 1) (Wilson *et al*., 2005). The eight-item CNAQ was developed from a longer, previously validated, tool using the Delphi technique (Crisp, 1997; Mathey, 2001). The aim of the research study was to develop a short and practical instrument that was able to identify adults in long-term care and in the community who were at risk of weight loss and malnutrition. Each item of the questionnaire, which is self-completed by the patient, includes five possible responses. Each response grades the severity of the symptom and scores between one and five, where lower scores indicate increased risk. Results from the study demonstrated that the CNAQ, and a four item shorter version termed the Simplified Nutritional Appetite Questionnaire (SNAQ) (Appendix 2), were both able

to predict weight loss in adults living in long term care and the community. Statistical analysis using Receiver Operating Characteristic curves suggested an optimum cut off point of 28 or less being predictive of at least 5% weight loss over six months for the CNAQ and 14 or less for the SNAQ. The sensitivity and specificity of the CNAQ at predicting 5% weight loss were both 80% and at predicting 10% weight loss, 82%. The four-item SNAQ wielded similar results; 81% sensitivity and 76% specificity for prediction of 5% weight loss and 88% sensitivity and 84% specificity for 10% weight loss. Further research is required to establish if the CNAQ could be used within the cancer population.

2.7 Summary

As discussed, malnutrition and the cachexia syndrome have many adverse physical and psychological consequences resulting in an increase in morbidity, treatment complications and overall mortality. Financially, within the health care system, this equates to higher treatment costs of complications, increased staffing levels and longer hospital stays. It is clear that the successful management of malnutrition and cachexia needs timely intervention and therefore early recognition of the problem. However, no agreed international definition of malnutrition or cachexia exists, meaning that progress in this important area of research is sluggish. Also, as a result, there is no consensus as to the most appropriate screening instrument to use to identify patients at risk of malnutrition and little work has been done thus far to develop a screening instrument for cachexia. A simple and practical screening instrument, validated within the cancer population and encompassing all elements of cachexia syndrome will help to move this work forward. Coupled with a multi-professional approach, this should help to improve treatment outcomes, functional capacity and quality of life for people with cancer.

2.8 Study aim, hypothesis and key objectives

2.8.1 Aim

The overall aim of this study was to develop a greater understanding of the complex factors that have an effect on, and can predict, weight loss in people with cancer, with the intention of influencing nutritional management strategies in clinical practice.

2.8.2 Hypothesis (Phases I and II)

A simple and practical screening instrument, with demonstrated reliability and validity, can predict clinically significant weight loss in people with lung or upper gastrointestinal cancer.

2.8.3 Key objectives

The key objectives for this project were to:

1. Obtain an estimate of the reliability of the CASQ.
2. Determine the predictive validity of the CASQ
3. Determine the optimal cut points and overall performance of the CASQ at predicting clinically significant weight loss over three months.
4. Propose an optimum screening instrument to predict clinically significant weight loss over three months.
5. Describe the experiences of people with lung or upper gastrointestinal cancer, and their carers, regarding the factors influencing weight change
6. Explore the causes and influencing factors of weight change in people with lung or upper GI cancer.
7. Propose a conceptual model of influences on weight change in people with cancer.
8. Identify areas for improvement regarding the nutritional management of people with cancer.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Introduction

The aim of chapter three is to outline the underlying theories of quantitative and qualitative research that were adopted for this project. In particular, the use of a mixed methods study design will be examined. Following on from this, the development and validation of health measurement scales, and the quantitative methods used within Phase I and II of the study are discussed. This chapter continues with an overview of the principles of qualitative research, in particular grounded theory, and the methods followed in the qualitative Phase III study. It concludes with a discussion of the ethical considerations of the study.

3.2 Theory of research methodologies

3.2.1 Research paradigms

A paradigm can be defined as a theoretical or philosophical framework. Within health and social care research, several paradigms have developed over the years. Tashakkori and Teddlie (1998) named positivism, postpositivism, pragmatism and constructivism as four important paradigms to discuss. Figure 3.1 demonstrates how these four paradigms interplay within the research cycle. Purist researchers who take the approach of positivism believe that quantitative research studies, using deductive reasoning, can determine a single truth with a cause and effect relationship. In addition, there is an understanding that the researcher's values and beliefs play no part in the process. During the mid 20th century, theorists began to question the assumptions of this paradigm, believing that understanding is constructed, and that the researcher's values and beliefs may influence the outcome (Schutz, 1967; Oakley, 1999). The postpositivist approach continues to utilise mainly quantitative methodologies and deductive reasoning. In addition, there is acknowledgement of how realism may influence the conclusions (Guba, 1990; Clark, 1998).

At the opposite end of the spectrum from positivism is the constructivist paradigm, where qualitative research methods are used to induce reasoning. The constructivist approach directly opposes that of the positivist, and, to a great extent, the postpositivist position. Constructivists believe that there are numerous realities and that it is not possible to differentiate between cause and effect (Guba and Lincoln, 1994). During the 1980s, these contrasting standpoints led to what has

been termed in the literature as, ‘paradigm wars’. Non-purist researchers however do believe that these paradigms can co-exist. From this concept of co-existence came a fourth paradigm, pragmatism (Howe, 1988; Datta, 1994). The pragmatic approach encompasses both quantitative and qualitative methodologies, focussing on the facilitation of human problem solving with an acceptance of reality (Carr, 2009). In healthcare research, using this pragmatic mixed methods approach, can aid understanding of the multi-dimensional and multi-faceted issues which exist within this complex field (Mason, 2006).

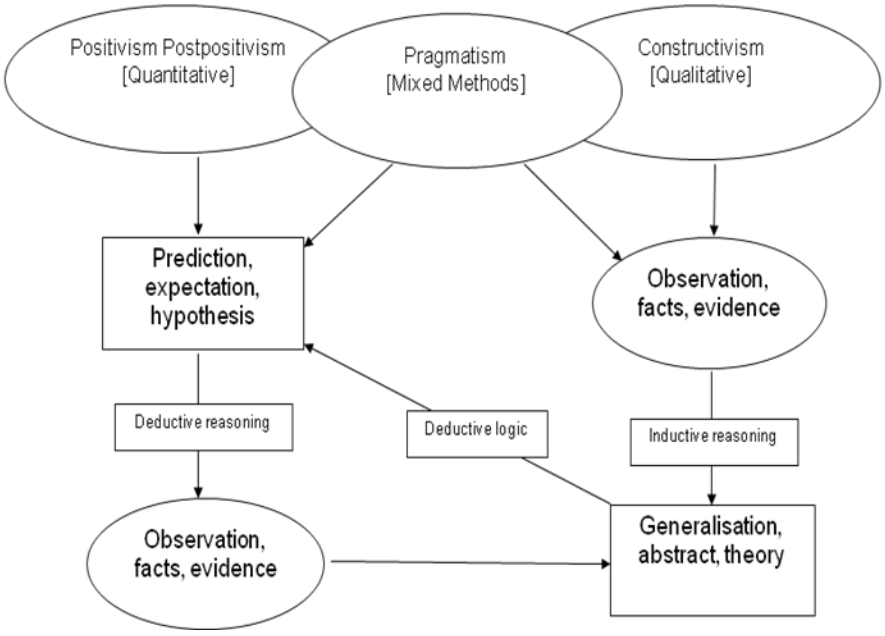

Figure 3.1: Research paradigms and their interplay with the research cycle (Adapted from Tashakkori and Teddlie, 1998).

3.2.2 Mixed method research

Mixed methods research can be defined as using quantitative and qualitative methods and data in a single study or series of studies, to investigate the same underlying concept (Leech and Onwuegbuzie, 2009). The advantages of such methodology are many. Jick (1979) discussed how a mixed method approach can allow for triangulation or cross-validation of results, providing a deeper, more holistic knowledge. Others debate whether cross-validation is truly possible in mixed method research, as such diverse paradigms cannot measure the same phenomenon (Sale *et al*., 2002). There is certainly agreement that methods can be combined for complementary purposes. Since its origin, the classification of mixed

method study design has become complex, with no agreed terminology. Despite this confusion, its use appears to be increasing in popularity, particularly within health and educational research. To help clarify the categories of research design, several authors have developed a 'typology' (Tashakkori and Teddlie, 1998; Johnson and Onwuegbuzie, 2004; Leech and Onwuegbuzie, 2009). Johnson and Onwuegbuzie (2004) describe a continuum of research design from mono-methods (quantitative or qualitative), through partially mixed, to fully mixed methods. A fully mixed design incorporates both quantitative and qualitative methods and data within the same phase of the study. A partially mixed design conducts quantitative and qualitative phases in their entirety, mixing the data at the interpretation stage. This description, aside from whether the studies are performed concurrently or sequentially, forms the basis for most mixed method designs. Whether the quantitative and qualitative methods have equal or dominant status is also added to the typology described by other authors (Leech and Onwuegbuzie, 2009).

3.2.3 Predicting weight loss in people with cancer: A mixed methods approach

A mixed methods approach to research can provide a deeper insight and superior understanding of the concept of interest (Johnson and Onwuegbuzie, 2004). Using both quantitative and qualitative methods to investigate and explore the causes and influencing factors of weight change in people with cancer, in a mixed method exploratory research design, should allow the qualitative data to explain, and provide a greater understanding of, the findings from the quantitative data (Ivankova *et al*., 2006). In line with this approach, the predicting weight loss study described in this thesis included three phases. Phases I and II were conducted sequentially and used quantitative methodology, principally to determine the reliability and the validity of the Cancer Appetite and Symptom Questionnaire (CASQ). Phase III was conducted concurrently alongside Phase II using qualitative methodology. It was designed to explore the influences on weight change in people with cancer. The underlying philosophical framework that was supported for this study was pragmatism. This was not solely based on the appropriateness of conducting a mixed methods study to answer the research question. Throughout there was certainly an emphasis on the importance of the outcome and how it might work in clinical practice. Taking this non-purist or compatibilist approach also stemmed from the belief that both the positivist and constructivist paradigms have their strengths and weaknesses. Using the principles of grounded theory, (Strauss and Corbin, 1994) the hope was that from the study would emerge a framework which can help us to understand the complex social processes which surround the issue of weight

loss in people with cancer. Integration of this with the results from the quantitative work had the potential to result in more rigorous conclusions and practical outcomes.

3.3 Quantitative research methods

Phase I and Phase II of the predicting weight loss study involved the psychometric testing of a health measurement scale, namely the Cancer Appetite and Symptom Questionnaire. To meet the key objectives listed below, the approach taken was quantitative in nature.

Key objectives for Phase I and Phase II were to:

1. Obtain an estimate of the reliability of the CASQ (Phase I).
2. Determine the predictive validity of the CASQ (Phase II).
3. Determine the optimal cut points and overall performance of the CASQ at predicting clinically significant weight loss over three months (Phase II).
4. Propose an optimum screening instrument to predict clinically significant weight loss over three months (Phase II).

Before describing the methodology that was followed for this part of the study, it is important to consider some of the theory behind the development and psychometric testing of health measurement scales.

3.3.1 Theory of health measurement scale development

A multitude of instruments have been developed to measure various subjective elements of health and disease. Several of these instruments, such as the McGill Pain Index are self-report measurement scales consisting of a series of items which collectively measure the same concept (Melzack, 1975). Others, particularly those aimed at measuring a multi-faceted phenomenon such as quality of life, for example the EORTC QLQ-C30, are multi-dimensional in that they measure a number of concepts which contribute to a person's quality of life (Aaronson *et al*., 1995). The subjectivity of the conditions that such instruments are attempting to measure, results in a complex development and validation process. In view of this, the first course of action for the researcher should be a review and evaluation of all existing instruments which have been designed to measure the same concept. Only when the possibility of using an existing reliable and valid tool has been excluded should a new one be developed. When developing a new instrument, the purpose for which it will be used is paramount and should help determine the characteristics of scale.

3.3.1.1 Developmental approach

Streiner and Norman (2008) describe the 'traditions of assessment' which have resulted in two measurement scale models; the categorical and the dimensional model. These models have emerged from the different approaches taken by medical, psychology and educational researchers. An example of an instrument developed using the categorical model is for the purpose of diagnosing a condition such as iron deficiency anaemia in order to then provide treatment. Responses to items on this type of instrument are likely to be dichotomous, yes or no, with resulting nominal (categorical) data. There are clear limitations to a model that categorises people as having the condition or not. Under these circumstances qualitative and quantitative information on the extent of such symptoms or attitudes is not obtained making evaluation of the condition, or comparison of severity, not possible.

The dimensional model theory is based on the work of Stevens (1946) and has traditionally been used in the psychology and educational disciplines. Stevens proposed that levels, defined as nominal, ordinal, interval and ratio, should exist within measurement scales. The reasoning for this is that the complexity of symptoms, attitudes, thoughts and feelings means that there is usually a scale to their magnitude. For example, answers to a question such as "do you feel nauseous before eating", could elicit several responses from "never", "rarely", "sometimes", "often" and "most times". To answer such a question with "yes", or, "no" would be difficult for most, as the respondent's state will likely fall along a continuum. As described by Streiner and Norman (2008), a greater number of response categories for each item may also result in an instrument with better precision as respondent error is likely to be lower. This is because, for example, if there are only three response categories there will be greater extremes between possible answers. Respondents may not be able to give the response that most closely matches their condition, consequently, the instrument will not be able to detect small changes in states. Unlike categorical models, instruments designed using the dimensional model do not classify people into, for example, cases or non-cases. In order to use this type of instrument diagnostically, consideration needs to be given to the optimum cut point (Altman and Bland, 1994). This would need to be determined based on research that tests the instrument. Nonetheless, the dimensional model does allow for comparison of severity of symptoms and conditions between subjects and for evaluation of change over time.

3.3.1.2 Characteristics of the Cancer Appetite and Symptom Questionnaire

The CASQ is an instrument based on the dimensional model of measurement scales. It consists of 12 items and each item has five possible response categories scored zero to four, where lower scores indicate a higher appetite and symptom burden. It is not possible to know the true interval between responses given in questions such as those in the CASQ. For this reason the data collected cannot be classed as interval or ratio data. The responses given by patients will in effect elicit continuous, ordinal data which is ranked. Therefore, the relationship between each of the responses can be ascertained in terms of whether a response category is greater or less than another. Although instrument scales which provide interval or ratio data allow for the most comprehensive, parametric statistical analysis, the results of those that elicit ordinal data, are often analysed using the same techniques. Debate is ongoing as to whether this is appropriate. Streiner and Norman (2008) conclude that providing the data from rating scales is not skewed, it can be analysed as interval data, without the introduction of bias.

As identified above, the CASQ has five response categories in each item. The ideal number of categories is an area which is often debated. Too many and the respondent could get confused, whilst too few may result in missing information, respondent measurement error and lack of precision (Streiner and Norman, 2008). A study by Hawthorne (2006) suggests that reducing the number of response categories from nine to five has no effect on the psychometric properties of an instrument designed to measure pain (Hawthorne, 2006). Findings of another study have established that seven to 10 categories are optimal in terms of the reliability of an instrument (Preston and Coleman, 2000). Streiner and Norman (2008) conclude that the optimum number of categories within an item should be between five and seven. However, it is also worth considering the literacy levels of the intended respondents, as scales with fewer responses may lead to improved psychometric properties of an instrument when used in people with very low literacy (Chachamovich *et al*., 2009). It may be assumed, from the supporting literature that the number of categories in each item of the CASQ is appropriate.

A further point to consider when aiming to reduce respondent error and improve response rates is the wording of questions and response categories. If an instrument is to be used with the general public, using plain English can improve understanding and completion of the instrument (Plain English Campaign, 2009). The wording of the CASQ was determined prior to this research study. It is therefore

not possible to know if this was an issue that was considered. When calculating the readability of the CASQ using the Flesch Reading Ease formula the resulting score was 79. This test rates the text on a 100-point scale with scores higher than 60 being considered as acceptable for literate adults (Dollahite *et al*. 1996). Although the CASQ does not appear to contain jargon, and is written using simple words and short sentences, the use of adjectival scales which include, for example, “often” or “rarely” must be considered. These words may have different connotations to respondents depending on their point of reference. Including an actual frequency, such as less than once a day may have helped to overcome this issue.

A final issue to discuss is the scoring of the instrument. All 12 items in the CASQ are scored in the same way, with equal weighting. Once completed by the respondent, the scores from each item are summed, giving a total score for the instrument. In this case possible scores ranged from zero to 48. This method is simple but consideration needs to be given to the fact that two individuals may, for example, have the same total score which has been derived from very different responses. An alternative is to weight the items dependent on their importance in measuring the concept. Importance may be judged by the investigator or expert, or ascertained using multiple regression techniques (Streiner and Norman, 2008). An alternative method is to ask respondents to self-weight items within the instrument dependent on how they perceive for example, the severity of their symptoms. There appears to be no clear answer as to whether weighting can improve the psychometric properties of an instrument (Locker *et al*., 2007; Streiner and Norman, 2008).

3.3.2 Psychometric testing of health measurement scales

Psychometric theory is likely to have originated in the late 19th Century when researchers such as Francis Galton developed mathematical techniques to measure intelligence (Galton, 1879). In recent times it has been used to measure a number of unobservable and subjective phenomena, for instance, attitudes, beliefs and personality. Within the healthcare setting, this has been extended to the development of scales to measure things such as quality of life, symptoms and experiences. For example, the EORTC QLQ-30 and the Functional Assessment of Cancer questionnaire are frequently used instruments developed to measure the quality of life and function in people with cancer (Aaronson *et al*., 1993; Cella *et al*., 1993). Two main theories exist with regard to testing of measurement scales; item response theory (IRT) and classical test theory (CTT). Both models are based on

mathematical techniques (Wilson *et al*., 2006). One key difference is that the information obtained through applying CTT relates to the instrument as a whole, whereas using the IRT model will elicit information at an item level.

Item response theory is a framework based on mathematical modelling which has developed over recent years (Harvey, 1999). Simplistically, IRT utilises a model which can determine the probability or 'ability estimate' of each item response based on the latent trait, such as anxiety, and the item parameters. What appear to be complex theory and analysis techniques may be what is holding back many healthcare researchers from using IRT. However it is likely that over the coming years, as agreed standards for use and reporting of IRT develop, its application will begin to increase within this field of research (Hays and Lipscomb, 2007).

Whereas IRT has only developed relatively recently, CTT has been the method of choice for many years (Jette, 1980; Cella *et al*., 1995). The foremost concepts of CTT are the reliability and validity testing of an instrument. The underlining principle is that the observed score obtained from an item in a measurement scale is equal to the true score plus measurement error. CTT assumes that for each item within the scale, the amount of measurement error is not associated with the true score, i.e. the difference in measurement error is the same irrespective of what the true score is and, the average measurement error for the instrument is zero (Streiner and Norman, 2008). Phase I and Phase II of the predicting weight loss study use the concepts of CTT to test the reliability and validity of the CASQ, as such the theory behind these concepts will be discussed in more detail in the following sections. In addition, some of the considerations which need to be given to the interpretation of information from CTT analysis will be discussed in subsequent chapters.

3.3.3 Phase I study methodology

Phase I of the predicting weight loss study was a short-term longitudinal study, with two test points one week apart. The objective of this part of the study was to estimate the reliability of the CASQ. Reliability is a measure of an instrument's reproducibility. As such, for an instrument to be reliable it should have the ability to produce consistent results over two or more time points, with a group of subjects in whom there has been no evidence of change (Streiner and Norman, 2008). Reliability can be estimated in several ways, depending on the type of instrument being tested. For this study, a measure of the internal consistency reliability and test-retest reliability of the CASQ was made. Details of these measurement

techniques are discussed below. Following this, the details of the Phase I study sample, recruitment, data collection and analysis are given.

3.3.3.1 Internal consistency reliability

Internal consistency reliability is a measure of the degree to which all items within an instrument are measuring the same concept (Bland and Altman, 2002). It is based on the correlations between the scores derived from the individual items in the instrument i.e. item-item correlation, and between the item scores and the instrument's total score i.e. item-total correlation. In order to estimate the internal consistency of an instrument, the Cronbach's alpha coefficient is often used. This is because Cronbach's alpha gives an estimate based on all possible correlations between the items in a scale (Bland and Altman, 1997). Although there is no agreed acceptable standard, the closer the resulting value is to one, the higher the internal consistency.

3.3.3.2 Test-retest reliability

Many instruments used within the healthcare setting, including the CASQ, are self-administered. In order to determine the stability of such an instrument over time, test-retest reliability is estimated (Bland and Altman, 2002). The procedure for this requires the administration of the instrument, to the same population, at two time points. The length of time between the time points is an area of debate and previous research has used anything from one hour to one year. It is thought that a retest interval of between two to 14 days is appropriate (Streiner and Norman, 2008). Once the scores from the items and instrument have been obtained, several statistical techniques can be employed to estimate the test-retest reliability of the instrument. Bowling (2002), suggests that for nominal data the kappa coefficient should be used, and for ordinal data, the weighted kappa coefficient. For interval data, Pearson's correlations should be calculated. As with the Cronbach's alpha coefficient, the closer the resulting value is to one, the higher the correlation and the better the reliability of the instrument. As will be discussed in Chapter Four, there are limitations to the interpretation of such correlations, with some researchers preferring to use the Bland-Altman type plot, defining the limits of agreement (Altman, 1991). A final, favoured measure of test-retest reliability is the intraclass correlation coefficient (ICC). Statistically, the ICC is a ratio of the variance between subjects to the total variability where the total variability is the sum of between subject variability and measurement error, or 'within subject' variance (Kirkwood and

Sterne, 2003). An ICC value equal to one suggests that there is no measurement error and therefore a perfect instrument.

3.3.3.3 Phase I sample

In the present study, the selected group members had a diagnosis of cancer and were likely to be clinically stable over the duration of one week, i.e. not at high risk of disease or treatment related appetite and weight loss. On a practical level, they were easy to access as they attended the hospital Monday to Friday for treatment. Table 3.1 shows the participant inclusion and exclusion criteria. Any patient receiving radiotherapy to the head, neck or upper gastrointestinal tract area and those with a condition impairing their ability to swallow were excluded as this could potentially have influenced their clinical condition and stability.

Table 3.1: Phase I study participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Adults, over 18 years of age	1. Receiving radiotherapy to the head, neck or upper gastrointestinal tract area.
2. Confirmed diagnosis of cancer	2. Any condition impairing their ability to swallow.
3. Receiving radiotherapy	3. Unable to provide written informed consent and therefore complete the questionnaire due to cognitive impairment.

The inclusion and exclusion criteria for the participants of the Phase I study are shown.

3.3.3.4 Phase I sample size

A sample size of 35 at two time points would allow detection of a correlation coefficient of 0.7 with 95% confidence intervals that exclude a lower limit of 0.5. (Streiner and Norman, 2008). This is at an appropriate level to determine the reliability of the CASQ.

3.3.3.5 Phase I participant recruitment

During September and October 2007, the medical notes of all patients undergoing radiotherapy treatment at Nottingham City Hospital Campus of The University of Nottingham Hospitals NHS Trust were reviewed by the superintendant therapy radiographer. Those who met the study inclusion criteria were offered a participant information sheet (Appendix 15) by the radiotherapy department staff. The number

of patients who declined to take an information sheet was not recorded. Anecdotally it was noted that a small number of female patients, who were having curative radiotherapy treatment post surgery for breast cancer, were concerned at being offered an information sheet which was aimed at people with cancer. A minimum of 24 hours later, potential participants were approached by the researcher, asked if they had any questions about the study and if they would like to take part. Written informed consent (Appendix 16) was obtained from those wishing to participate. Data was not collected regarding the number of patients who declined to take part in the study, and their reasoning, at this point.

3.3.3.6 Phase I data collection

At time point one, participants were asked during their hospital visit to self-complete the CASQ. The instruction they received was to answer the 12 questions by ticking the box that most closely reflected their experience of appetite and symptoms at that present time. The completed questionnaires were put in an envelope by the patient and placed in a box in the radiotherapy department waiting room. At their visit one week later, time point two, participants were again asked to complete the CASQ, this time also noting if anything had affected their appetite and symptoms over the previous week. Demographic information including date of birth, gender, diagnosis and Eastern Cooperative Oncology Group (ECOG) performance status (Appendix 17) were documented by the researcher.

3.3.3.7 Phase I data analysis

The CASQ was completed in its entirety by all participants. For data analysis purposes, a score of zero to four was assigned to answers within each of the 12 items on the CASQ. As items four, eight, eleven and twelve were worded in the opposite direction to the other questions the scores were re-coded accordingly. A score of four was given to the answer which represented no symptom or appetite problems. Hence, low scores represented more appetite and symptom problems. To estimate the reliability of the CASQ, the internal consistency reliability and the test-retest reliability were determined. Cronbach's alpha co-efficient was used to examine the internal consistency reliability of the CASQ. Test-retest reliability was determined from a number of estimates including Pearson's correlations, a Bland-Altman plot and the intraclass correlation coefficient. All data was analysed using SPSS version 14.5 and STATA version 9.

3.3.4 Phase II study methodology

The Phase II study involved a longitudinal observational study with two test points three months apart. It was conducted following the completion of the Phase I work. One of the key objectives of this part of the study was to establish the predictive validity of the CASQ in terms of weight loss. Validity *per se* can be defined as the extent to which an instrument measures what it is supposed to measure. Statistically, it is the degree of confidence that can be placed on the inferences that arise from the test scores (Streiner and Norman, 2008). There are a number of techniques for determining the validity of a measurement scale such as construct, convergent, discriminant and criterion validity (Bowling, 2002). Predictive validity is a form of criterion validation and for this reason an explanation of criterion validity has been given below. When developing the CASQ, as described in Chapter One, the content validity of the instrument was also determined. Therefore, the principles of content validity have also been discussed here. This section concludes with details of the Phase II study sample, recruitment, data collection and analysis.

3.3.4.1 Content and face validity

Face validity can be defined as how an instrument looks and whether it covers what we think it should. This is different to content validity which considers if all factors relevant to the subject being measured have been included (Bland and Altman, 2002). To many researchers, the technique used to determine content and face validity is similar. Both involve an expert or group of experts giving their subjective judgement as to whether items within a scale are relevant, appropriate and clear. For this reason, some have questioned its use within psychometric testing (Fitzpatrick, 1983). Indeed, assessment of face validity rarely involves more than the process described above. In contrast, assessment of content validity appears to have more substance. Lynn (1986) describes how content validity can be determined using a two stage judgement quantification process. From this process the content validity index (CVI) is calculated as a proportion of expert panel members who rate the item as relevant. As this technique does not adjust for chance agreement, more recent work has been conducted defining how the kappa coefficient can be used to determine a more accurate item-level content validity index (Polit *et al*., 2007).

3.3.4.2 Criterion validation

The technique for determining criterion validity is the comparison or correlation of the new measurement scale with an existing and validated 'gold standard' measure (Bland and Altman, 2002). Concurrent and predictive validity are examples of criterion validity.

Concurrent validity can be established by administering the new and established gold standard measurement scales to the same population at the same time or within a short time frame of each other (Streiner and Norman, 2008). A question that must be asked is, if there is already a gold standard measure, then why is another one needed? Possible answers to this question, and therefore reasons for developing a new test, may be that the existing test is expensive, time consuming or dangerous. For example, to diagnose colorectal cancer, the gold standard is colonoscopy. Results of a study comparing colonoscopy to a new, less invasive test, which involves swallowing and excreting a colon capsule endoscopy are promising (Schoofs *et al*., 2006). Concurrent validity can be determined by estimating the correlation between the results from the new and gold standard test (Kirkwood and Sterne, 2003). To analyse the results from the two tests, where outcomes are dichotomous, a simple four-fold cross-tabulation can be used. For continuous data the Pearson's correlation coefficient can also be calculated. In addition, the sensitivity and specificity of the new test can be estimated. As defined by the gold standard test, if the new test has high sensitivity it will be able to detect accurately most or all of those subjects who are at risk, or diagnosed with the condition. In addition, if the new test has high specificity, it will correctly identify those who are not at risk, or free from the condition (Streiner and Norman, 2008).

When testing the predictive validity of a new measurement scale, the criterion which it has been developed to predict, will not be evident until some time in the future, when it will be determined by the gold standard test (Streiner and Norman, 2008). One reason for developing a new instrument with predictive validity is that in some circumstances it may be advantageous to intervene in a proactive rather that reactive way. With established tests, the outcome may not be evident until it is too late to do anything about it. This is often the case with weight loss in people with cancer. Being able to predict those patients who are going to lose weight, with intervention, may prevent or reduce the problem from occurring. Predictive validity is expressed as a four-fold cross-tabulation or Pearson's correlation, between the results from the new measurement scale and those obtained, in the future, by the

gold standard test (Streiner and Norman, 2008). An important consideration when conducting predictive validation studies is that practice is not changed due to the outcome from administering the new instrument. Should this occur, the correlations are likely to be lower due to having a reduced or truncated sample. As with concurrent validation, the sensitivity and specificity of the new instrument can also be determined.

3.3.4.3 Phase II sample

Patients with lung or upper GI cancer were chosen as they are known to have a high incidence of nutritional deficiencies (Stratton *et al*., 2003). Table 3.2 shows the participant inclusion and exclusion criteria. As the aim was to develop a screening instrument that would predict weight loss, those who were already malnourished, as indicated by a Malnutrition Universal Screening Tool (MUST) score of two or more, were excluded (Stratton *et al*., 2004). Any patient with oedema, or ascites was excluded on the basis that it would have been difficult to ascertain their true 'dry' weight. Patients were not excluded on the basis of their treatment plan or stage of disease.

Table 3.2: Phase II study participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Adults, over 18 years of age 2. Confirmed diagnosis of primary lung or gastrointestinal cancer.	1. Lost > 10% of their pre-illness stable body weight 2. Lost between 5 and 10% of their pre-illness stable body weight with a BMI < 20kg/m^2 3. BMI < 18.5 kg/m^2 4. Presence of oedema or ascites 5. Receiving enteral tube feeding or parenteral nutrition 6. Unable to provide written informed consent and therefore complete the questionnaire due to cognitive impairment 7. Not able to be weighed

The inclusion and exclusion criteria for the participants of the Phase II study are shown.

3.3.4.4 Phase II sample size

When developing a screening instrument, a minimum of 10 participants is required for each item to be tested (Peduzzi et al., 1996). It was the intention to test 16 items in the screening tool; 12 items of the CASQ, C-Reactive Protein, plus baseline measurements for body mass index, percentage weight loss and the MUST score.

Thus, a sample of 160 was required. Within oncology and palliative care settings research suggests that a 15% attrition rate is typical (Addington-Hall, 2002). Allowing for this attrition rate a recruitment target of 185 participants was set.

3.3.4.5 Phase II participant recruitment

Participants were recruited from the oncology out-patient clinics at Nottingham City Hospital Campus between October 2007 and February 2009. Depending on the format and running of the clinic that they were attending, participants were recruited in one of two ways. As several clinics were running concurrently, and with only one researcher, it was not possible for all patients attending the clinics to be screened. Therefore patients were approached in an ad hoc manner, on the basis of practicality and convenience. For the majority of patients, on arrival at clinic, they were approached by the researcher and given a letter (Appendix 18) from their clinician informing them that they would be screened for risk of malnutrition using the MUST. The letter also indicated to them that if their weight was stable they would be asked if they were interested in taking part in the study. In most of the clinics the patients' weight and height were routinely measured by a member of the clinic staff. Where this was not the case the researcher ensured that this was done. At this point, with verbal agreement from the patient, the MUST score was calculated by the researcher, and those who met the inclusion criteria, were asked to read a participant information sheet (Appendix 19) whilst they waited to see their doctor. Usually following their consultation, for those wishing to take part, informed written consent (Appendix 20) was taken by the researcher and the CASQ administered immediately.

The alternative method involved the patient, after their consultation, being informed by their doctor about the study and being asked if they were happy to speak to the researcher for more details. At this point their MUST score was calculated by the researcher and those who met the inclusion criteria, were asked to read the participant information sheet. Again, for those wishing to take part, informed consent was taken by the researcher and the CASQ administered. A minority of patients were unable to take part on the day due to time constraints, but were keen to participate. For this group an appointment was made by the researcher to see them at another time, usually within two to three days, when they were attending the hospital for chemotherapy. A log of patients who were approached, screened and recruited was maintained throughout the study to avoid re-approaching those who had already been seen. Those patients who were identified as being at risk of

malnutrition based upon the MUST score, i.e. a score of two or above, were highlighted to the clinician in clinic and a copy of the MUST documentation was put in their medical notes (Appendix 21). The clinicians were advised to follow their normal practice with regards to the nutritional management of the patient. All participants were offered a standard written advice leaflet about ways to improve their nutritional intake (Appendix 22).

3.3.4.6 Phase II data collection

Participants were asked to self-complete the CASQ. They were instructed to respond to the questions considering how they had felt over the last day or two. As many of the patients were having a blood sample taken on the recruitment day for chemotherapy bloods, C-Reactive Protein analysis was requested from the same sample. All other consented subjects were given a blood test form and invited to go to the clinic phlebotomist. If they were unable to wait they were asked to visit their GP clinic at their earliest convenience. All blood samples were analysed by the Nottingham University Hospitals NHS Trust pathology laboratory.

Demographic information, diagnosis and stage of disease, treatment plan, performance status as well as weight, height, previous weight and MUST score were documented by the researcher. With the participants' permission, their G.P.s were informed of their involvement in the study (Appendix 23).Twelve weeks later, plus or minus one week, participants' weights were measured and percentage weight change calculated. The majority of subjects were attending the hospital within this time frame and had their weight measured in clinic. As it was not practically possible to visit all of those who did not have a hospital appointment, approximately ten percent of patients were asked to self-report their weight based on measurements taken from their own, or G.P practice's, weighing scales. Participants that were unable to weigh themselves within the time frame were excluded from the data analysis. Previous research suggests that, when asked to self-report, men and women, particularly those who are overweight, are inclined to under-estimate their body weight (Spencer *et al*., 2002; Gorber *et al*., 2007). However, unlike in the present study, this work has focussed on an overweight population and does not take into account the use of weighing scales. Although self-reporting of weight in the present study could have led to a degree of imprecision when obtaining the follow up weight, it was felt that the extent of this had been minimised. In addition, the data was primarily used to categorise patients into groups of percentage weight loss or BMI.

Further information, with regard to date of death for those study participants who had died, was collected using the hospital data base on the 25th of August 2009.

Outcome measures

The primary outcome measure was percentage weight loss over the three month study period. Additional key outcome measures taken at baseline were:

1. Responses to the 12 items on the Cancer Appetite and Symptom Questionnaire
2. C-Reactive Protein serum concentration.
3. Malnutrition Universal Screening Tool Score.

3.3.4.7 Phase II data analysis

As in Phase I of the study, for data analysis purposes, a score of zero to four was assigned to answers within each of the 12 items on the CASQ. As items four, eight, eleven and twelve were worded in the opposite direction to the other questions the scores were re-coded accordingly. A score of four was given to the answer which represented no symptom or appetite problems. Hence, low scores represented greater impairment. To compare the significance of the responses to the CASQ from the two tumour groups, the Mann Whitney U test was used. Pearson's and Spearman's correlations established the predictive validity of the individual items of the CASQ and the total score in terms of percentage weight change. The optimal cut point for the instrument, and the sensitivity and specificity of each cut point, were determined from Receiver Operating Characteristics (ROC) curve analysis. Positive and negative predictive values were also estimated at each cut-off. This analysis was conducted for both 5% and 10% weight loss. Reasoning for this was that although guidance from NICE (2006) suggest a weight loss of greater than 10% to be of clinical significance, others have associated a weight loss of greater than only 5% as having adverse outcomes (Evans *et al*., 2008).The level of agreement of the CASQ results at predicting those people who were at risk of malnutrition was compared with results from the pre-existing validated screening instruments, the MUST, MST and from C-Reactive Protein. This was evaluated using cross-tabulations and the proportion of agreement determined. ROC curve analysis was also used to establish how the CASQ performed when predicting 5% and 10% weight loss compared with the other screening instruments.

Exploratory multiple linear regression analysis, using a backward variable selection process, was used to build a model of the optimal set of variables that could

comprise a screening instrument. Variables were retained where $P < 0.10$ for log-likelihood ratio tests. Cox proportional hazard survival regression was used to determine if the CASQ had predictive validity in terms of length of survival post diagnosis. All data was analysed using SPSS version 16.0 and STATA version 9.

3.4 Qualitative research methods

Phase III of the predicting weight loss study was a qualitative exploratory study conducted following the principles of the Straussian approach to grounded theory (Strauss and Corbin, 1994). The key objectives were to:

1. Describe the experiences of people with lung or upper gastrointestinal cancer, and their carers, regarding the factors influencing weight change.
2. Explore the causes and influencing factors of weight change in people with lung or upper GI cancer.
3. Propose a conceptual model of influences on weight change in people with cancer.
4. Identify areas for improvement regarding the nutritional management of people with cancer.

An understanding of the origin and theory of qualitative research is important for any researcher wanting to participate in this type of work. This section will discuss some of the philosophy of qualitative research and, in particular as they are followed in this study, the principles of grounded theory. The section will conclude with a description of the methods followed in Phase III of this study.

3.4.1 Qualitative research traditions

Pope and Mays (1995) describe the goal of qualitative research as “the development of concepts which help us to understand social phenomena in natural (rather than experimental) settings, giving due emphasis to the meanings, experiences and views of all participants”. To achieve this goal there are several methodological approaches, or traditions, which can be followed. All traditions share the same underlying characteristics of qualitative research. Included in this is that the researcher holds the belief of the existence of multiple realities and plays an active role in the study. Also, that they have a commitment to understanding each participant’s individual perspective. The chosen approach may be determined by the type of research question which is to be answered. Some of the traditions which can be considered include grounded theory, phenomenology and ethnography. The

principles of grounded theory were followed in the present study to describe and explore the influences on weight change in people with cancer, with the overall aim being to guide intervention to improve the patient experience. As will be discussed in the next section, this tradition allows for theory on social processes to be constructed rather than, for example, the phenomenological or ethnographical methods which, are purely descriptive in their interpretation of lived experience or culture (Speziale and Carpenter, 2003).

3.4.2 Principles of grounded theory

Grounded theory was discovered by social scientists Glaser and Strauss in the 1960s (Glaser and Strauss, 1967). The underlying principle of grounded theory is that new theories are developed from a systematic inductive, constant comparative, analysis of the data. These theories can then be used not only to advance understanding within that specific field of study, but also to be able to predict and explain human behaviour. Grounded theory differs from the other traditions in several ways. Firstly, it aims to develop theories on social processes rather than specific phenomena. In particular, it looks at how individual complex interactions lead to diversity within social processes. Secondly, the analysis of data commences as soon as it has been collected and, as a consequence, the sampling of participants, as well as the research schedule, may be adapted throughout the course of the study to focus on more pertinent points. Grounded theory is widely used within health and educational research and has been reported as the qualitative methodological approach of choice (Miller and Fredericks, 1999). Despite this, it has attracted criticism from some. Thomas and James (2006) highlight the limitations of the approach. A key area of disapproval is the rigidity of the analysis process, resulting in the potential for theory to be invented rather than discovered. For the novice researcher, possibly drawn to using grounded theory because of its structured approach, an understanding of these limitations will help to improve the validity and reliability of the study.

From the time when grounded theory was first described by Glaser and Strauss, some of the fundamental aspects of this method have diversified. In part this has been due to the founders developing differing views regarding the detail of this research approach. Heath and Cowley (2004) describe some of the main differences between the two researchers' ideas. In summary, it seems that these are mainly methodological, rather than ontological or epistemological, in nature. In other words, both accept that there are multiple variations of reality regarding social

processes and both believe that new knowledge can emerge from the generation of theory. It is the techniques that are employed for the purpose of data analysis which differ.

3.4.2.1 Grounded theory data collection

Data collection begins with the sampling of participants. Within qualitative research studies, purposeful and theoretical sampling are widely used techniques. Although in some of the literature the terms appear to be used inter-changeably, there are pronounced differences between the two (Coyne, 1997). One of the key principles of grounded theory is the employment of theoretical sampling (Glaser, 1978). Here the researcher collects, codes and analyses data from the start of the study. Emerging theories direct the sampling of future participants and, as such, sample size cannot be pre-determined. There is the acknowledgement that in the initial stages purposeful sampling will need to be used to enable data collection to commence. As such, these participants will be selected on the basis of, for example, their gender, age or lived experiences. Data collection continues until saturation is reached and no new codes are emerging from the data.

Interviews, observations and focus groups are frequently used enquiry techniques within qualitative research, although the exact method may be determined by the research question and chosen tradition. Unlike observation, talking to people allows one to gain an insight in to their individual perspective, emotions and feelings. Patton (2002) describes three structures of interviews which can be employed to help elicit the required information. The standardised open-ended interview, or structured interview, is a set of pre-determined questions asked to all participants. This allows for little flexibility in terms of probing for further information but is useful if a consistent approach is required. The general interview guide, or semi-structured interview, consists of an outlined schedule of questions. With this, method deviations and further exploration of themes brought up by the interviewee can be explored. The third type is the informal conversational interview, or un-structured interview. Here there are no pre-determined set of questions and no specific agenda. Conversation flows in a natural manner. As with all methods of inquiry the quality of the data collected is somewhat dependent on the skills of the interviewer. There is direction within the literature in terms of the suggested ordering of questions and the communication skills which the researcher should aim to use (Whyte and Whyte, 1984; Patton, 2002).

3.4.2.2 Grounded theory data analysis

As previously highlighted, grounded theory uses a constant comparative approach to data analysis. Initially, as described by Glaser and Strauss (1967), this was a two stage process. The generation of multiple codes from the data is followed by reduction and comparison of the data from which emerges a conceptual framework around the core themes. Through continued modification and interpretation this framework can develop from a model, which describes and explains basic social and psychological processes, to a theory (Speziale and Carpenter, 2003). One of the main differences with the Straussian model is that it takes a more systematic approach to analysis (Heath and Cowley 2004). An intermediate phase termed 'axial coding' is added where the initial codes are then reduced down in number by categorising them into similar concepts. The appropriateness of this, in terms of the researcher 'choosing' the key themes at an earlier stage of the analysis, has been highlighted as a limitation (Heath and Cowley, 2004).

3.4.2.3 Trustworthiness in qualitative research

Discussion of validity or rigor of qualitative research is an ongoing debate (Creswell and Miller, 2000). To determine the trustworthiness of qualitative research, Lincoln and Guba (1985) describe four questions that should be asked. Firstly, what is the credibility, or the level of confidence that we can have that the study findings are indeed the 'truth'? Secondly, do the findings have transferability, i.e. what inferences beyond the study population can be made? Thirdly, do the findings have dependability, would they be the same if the study was to be repeated? Finally, to what extent may the findings have been influenced by the researcher? Systems that can be used to influence the trustworthiness are described in the literature (Patton, 1999; Mays and Pope, 2000; Creswell and Miller, 2000). These include methodologically developing analysis techniques to test for alternative explanations, including the use of triangulation, as well as determination of the credibility of the researcher. As the researcher acts as the data collection tool, analysis of their role, termed researcher reflexivity, can identify their belief systems, assumptions and any areas of bias. Additional methods may also involve the participants reviewing the interpretation of findings to ensure that it truly reflects their perspective.

3.4.3 Phase III study participants

Potential interviewees were those patients with lung or upper GI cancer, and their partner or carer, who were attending the out-patient clinics at Nottingham City Hospital and who were recruited into Phase II of the study.

3.4.4 Phase III sampling, recruitment and consent

From August 2008 to February 2009, following ethical approval of the Phase III study, participants recruited in to Phase II of the study were asked to indicate on the consent form if they agreed to being interviewed if selected. Following the principles of grounded theory, the aim was to use theoretical sampling techniques. As such, the final sample size could not be predicted. Initially, to allow data collection to commence, sampling was purposeful. Potential interviewees were chosen on the basis of their diagnosis and level of weight loss over the three month, Phase II, study period. Potential participants were approached by the researcher in the oncology out-patient clinic, or by telephone following their consultation, and invited to take part in the interviews. Where a partner or main carer was identified by the patient, they too were asked if they were interested in participating. If they were in agreement, a volunteer information sheet (Appendix 24) was given or posted out to them. It was envisaged that including the partner or carer would add to the depth of information, particularly regarding indicators of weight loss, appetite and food preparation. Following initial analysis of the data, rather than only including those people who had lost more than five percent of their body weight during the study period, theoretical sampling led to the inclusion of patients who had not lost a significant amount of weight. It was thought that this would provide information on strategies used by participants to maintain weight.

3.4.5 Phase III data collection

Interviewees were asked to attend the hospital at a time convenient to themselves, or they were given the option to be visited at home by the researcher. Prior to the interview commencing, informed written consent was given by the interviewee (Appendix 20) and, where appropriate, their partner or carer (Appendix 25). The interview process was explained by the researcher with the understanding that if at any point they wanted to stop they were able. Interview length was not constrained and varied from 17 to 70 minutes. All followed the same semi-structured format (Appendix 26) and began by asking interviewees to describe how their diagnosis of cancer had been made and the treatment that they had received to date. This was to help establish a time line of their weight prior to diagnosis, to current day. Interviewees were then asked to recall their experiences or observations of weight change, particularly regarding any signs and factors that contributed to weight loss. Information about the amount, type and source of any dietary advice that they had received was also gathered as was their experiences of any influences on ability to

comply. To avoid leading the interview, open questions were used by the researcher. In addition, where appropriate, probing questions were asked to gain more depth to the information discussed. Subsequent to the preliminary analysis of the first two interviews, the schedule was amended. Interviewees were asked to describe the information they would give to someone in a similar position with regards to the initial signs of weight loss and/or how to minimise weight loss.

At the end of the interview patient participants were asked to once again complete the CASQ. This was to help gauge any potential changes in appetite and symptom burden from when they first joined the study.

Within 24 hours of each interview, field notes were documented by the researcher. These included any thoughts about how the interviewees had responded, emotions expressed and underlying instincts regarding the key points raised.

All interviews were digitally recorded and then transcribed verbatim by an assistant. Following this, the researcher went through all recordings and transcripts to check for accuracy and amendments were made where necessary. To ensure anonymity, false names were assigned to participants as well as any other family members, friends or health care workers who had been named in the conversation.

3.4.6 Phase III data analysis

Data organisation and retrieval was managed using the qualitative software package NVivo 8. Using techniques described within the tradition of grounded theory, the data was analysed to highlight similarities or differences between each participant's experience with regards to a particular topic. Initially transcripts were read and re-read. Multiple codes were then generated from the transcript data until saturation was reached and no new codes were emerging, at this point data collection ceased. More specifically, this stage of the analysis involved exploring small sections, sentences and paragraphs, of each transcript to establish what was happening in the data. Axial coding followed where codes were reduced in number and categorised into similar concepts. Relationships between the categories and sub-categories were established and checked within, and across, each of the transcripts. Finally, summarisation and interpretation of key categories led to the emergence of core categories. From this, a conceptual framework was proposed.

3.5 Ethics

3.5.1 Ethical approval

The protocol and supporting information (Appendix 27) for all three phases of the study were given ethical approval by the Local Research Ethics Committee (Appendix 28) and the Research and Development Department at The University of Nottingham Hospitals NHS Trust (Appendix 29). The NHS Trust's Oncology Clinical Trials Strategy Group also approved the study. Phases II and III were adopted by the National Cancer Research Network and were included within their portfolio of studies.

3.5.2 Ethical issues

The study was conducted in line with the Good Clinical Practice (GCP) guidelines (International Conference on Harmonisation, 1996). All patients and, where appropriate, their carer, gave informed written consent to take part in the study. To ensure anonymity and confidentiality all information about participants was entered onto a database in an anonymised form. Access to the database was restricted to authorised personnel and password protected. All hard copies of forms and questionnaires were kept in the research office which was locked when not in use.

The main ethical issue for the study was that during Phase II potential participants were not given 24 hours to decide if they wished to take part. Justification for not giving longer was that if patients were identified at clinic as being eligible to participate they would be given the information sheet to take home. Those that decided to take part would then be required to come back to the hospital in a few days time to be consented, complete the CASQ and have a blood test. This would be on average a 10 to 15 minute appointment, for which there would be travel cost implications as well as the potential to increase levels of inconvenience and stress for the patient. Ethical approval was obtained to give participants as long a time period that was practical within the clinic setting between receiving the information sheet and being asked to give consent. There were minimal risks to participants recruited to the study. However, it was acknowledged that this was a vulnerable group of people, many having recently been diagnosed with a terminal condition. Discussing their condition and symptoms for some may have been emotionally distressing.

CHAPTER 4: PHASE I: RELIABILITY TESTING OF THE CANCER APPETITE AND SYMPTOM QUESTIONNAIRE

4.1 Introduction

Reliability testing is a key step in the development and evaluation of any measurement scale (Bland and Altman, 2002). Estimating reliability will determine the amount of error which is intrinsic to a screening instrument. The outcome from such testing may establish if an instrument will give reproducible results when administered to a specific population. If the Cancer Appetite and Symptom Questionnaire (CASQ) is to be of value within the clinical setting, reliability is therefore an important factor to consider.

Phase I of the predicting weight loss study was a short-term longitudinal study, with two test points one week apart. The study sample included clinically stable adults diagnosed with cancer. The key objective was an estimate of the reliability of the CASQ. For a self-reported instrument such as the CASQ, test-retest and internal consistency were estimated as appropriate measures of reliability.

The results of the analysis of the Phase I study data is presented in the subsequent section of this chapter. What follows is a discussion of the results specifically related to the estimated reliability of the CASQ.

4.2 Phase I results

4.2.1 Demographics

Fifty-one potential participants were approached, 38 consented to take part and all 38 completed the study. Twenty were female (53%) and the mean (SD) age was 60 (11.3) years. The most common diagnosis was breast cancer (50%), then prostate cancer (39%), bladder cancer (8%) and rectal cancer (3%). Thirty- seven participants had an Eastern Cooperative Oncology Group (ECOG) performance status of zero, and one a performance status of one. At time point two, four of the participants noted an event over the previous week that had affected their appetite and/or symptoms. In pursuit of a stable population on which to test the reliability of the CASQ, these four subjects were therefore excluded from the test-retest analysis.

4.2.2 Mean scores and differences

For the remaining participants (n=34), the mean (SD) total CASQ scores were 34 (4.7) and 33 (4.4) at time point one and two respectively. The range of scores was from 22 to 42 at time point one, and 24 to 40 at time point two.

4.2.3 Internal consistency

Internal consistency quantifies the extent to which all items in an instrument measure the same concept. In effect, this indicates if and how the items are correlated with each other. To determine the internal consistency between the 12 items of the CASQ, Cronbach's alpha was calculated (Table 4.1). Cronbach's alpha estimates reliability based on an average of all possible correlations between items. Although there is no agreed acceptable level, a value of 0.7 to 0.8 is deemed satisfactory by most researchers (Streiner and Norman, 2008). In addition to calculating the Cronbach's alpha coefficient for the 12 item CASQ, it was also calculated for each of the three domains, i.e. questions one to four relating to appetite, questions five and six about food intake and the remaining questions about symptoms. To determine if any of the CASQ items were reliability reducing, the Cronbach's alpha coefficients for each of the remaining 11 item CASQ models were also calculated (Table 4.2). Generally the Cronbach's alpha coefficients at each time point were similar. For all models, except the one containing only the food intake questions, the Cronbach's alpha coefficients met the acceptable level.

Table 4.1: Cronbach's alpha coefficients for the CASQ questions

CASQ questions	Cronbach's alpha coefficient Time point 1	Time point 2
1 to 12	0.76 (95%CI 0.63 to 0.86)	0.74 (95% CI 0.60 to 0.85)
1 to 4 Appetite	0.72 (95%CI 0.54 to 0.84)	0.82 (95% CI 0.70 to 0.90)
5 to 6 Food intake	-0.40 (95%CI -1.69 to 0.27)	-0.18 (95%CI -1.26 to 0.39)
7 to 12 Symptoms	0.65 (95%CI 0.45 to 0.80)	0.72 (95% CI 0.55 to 0.84)
1 to 4 and 7 to 12 Appetite & symptoms	0.80 (95%CI 0.68 to 0.89)	0.78 (95% CI 0.65 to 0.87)

Calculated at time point one and time point two, the Cronbach's alpha coefficient for the 12 item CASQ is shown, along with the calculated coefficient for each of the three domains; appetite, food intake and symptoms. The Cronbach's alpha coefficient for the 10 questions relating to appetite and symptoms is also shown.

Table 4.2: Cronbach's alpha coefficients for the 11 item CASQ models

CASQ question removed	Cronbach's alpha coefficient of 11 item model Time point 1	Time point 2
1 (Appetite)	0.71 (95% CI 0.56 to 0.83)	0.71 (95% CI 0.55 to 0.83)
2 (Satiety)	0.72 (95% CI 0.56 to 0.83)	0.71 (95% CI 0.55 to 0.83)
3 (Hunger)	0.76 (95% CI 0.62 to 0.86)	0.74 (95% CI 0.59 to 0.85)
4 (Enjoyment)	0.72 (95% CI 0.56 to 0.83)	0.70 (95% CI 0.54 to 0.83)
5 (Meals)	0.75 (95% CI 0.62 to 0.86)	0.73 (95% CI 0.59 to 0.84)
6 (Snacks)	0.80 (95% CI 0.69 to 0.88)	0.78 (95% CI 0.66 to 0.87)
7 (Taste)	0.74 (95% CI 0.60 to 0.85)	0.72 (95% CI 0.57 to 0.84)
8 (Taste change)	0.72 (95% CI 0.57 to 0.84)	0.69 (95% CI 0.52 to 0.82)
9 (Nausea and vomiting)	0.73 (95% CI 0.59 to 0.84)	0.70 (95% CI 0.54 to 0.83)
10 (Mood)	0.75 (95% CI 0.61 to 0.85)	0.70 (95% CI 0.54 to 0.83)
11 (Energy)	0.72 (95% CI 0.57 to 0.84)	0.75 (95% CI 0.61 to 0.85)
12 (Pain)	0.75 (95% CI 0.61 to 0.85)	0.76 (95% CI 0.62 to 0.86)

As calculated at time point one and time point two, the Cronbach's alpha coefficient, and 95% confidence intervals, for each of the 11 item CASQ models is shown.

4.2.4 Test-retest reliability: Measurement of agreement

4.2.4.1 Correlations

A scatter plot was drawn to determine the correlation of the results given by each participant at time point one and time point two. Figure 4.1 shows the line of regularity with a high positive correlation between the results. Using Pearson's correlation method, $r = 0.80$ ($P<0.01$).

4.2.4.2 Bland-Altman plot

To determine the extent of agreement between the total CASQ scores at the two time points, the results were plotted on a Bland-Altman plot (Figure 4.2). This type of plot allows a graphical representation of the between time point differences among the CASQ scores. On the Y axis, for each participant, the difference between their total CASQ scores at time point one and time point two is plotted, and on the X axis the mean of these two scores. The mean difference of the scores between the two time points was -0.20 (95% CI = -1.21 to 0.80), with a within subject standard deviation of the differences of 2.91. The upper limit of agreement was 5.62, and was estimated as plus 1.96 standard deviations from the mean. The lower limit of agreement, estimated as minus 1.96 standard deviations from the mean, was -5.90. No obvious relationship could be seen between the differences and the mean and there was a random scatter around zero. As 95% of the differences fell between the limits of agreement we can assume that the differences are normally distributed (Bland and Altman, 1986).

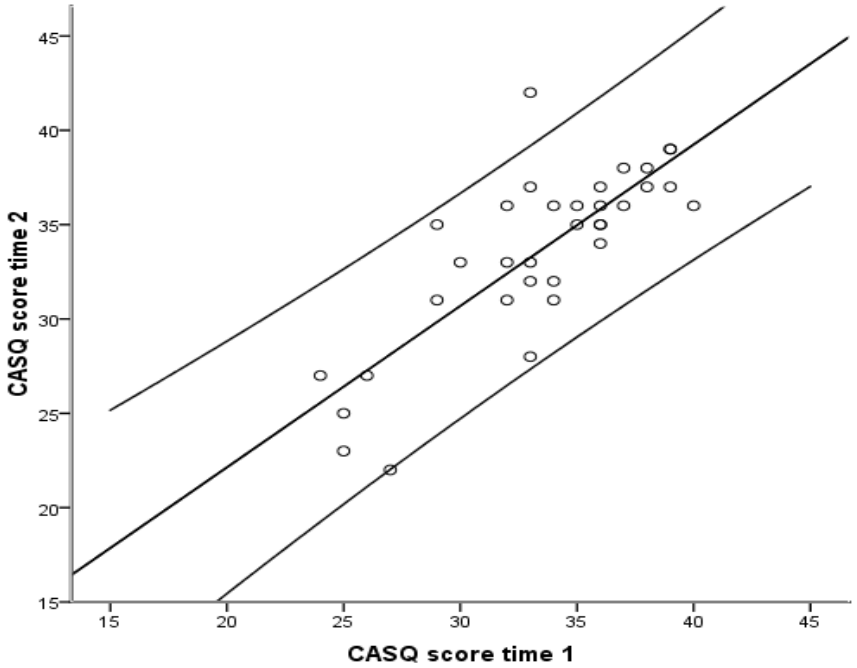

Figure 4.1: Agreement between total CASQ score completed at time point one and time point two, one week apart. For this positive correlation r = 0.80 (P < 0.01). The 95% confidence intervals demonstrate that the majority of the scores fall within these parameters.

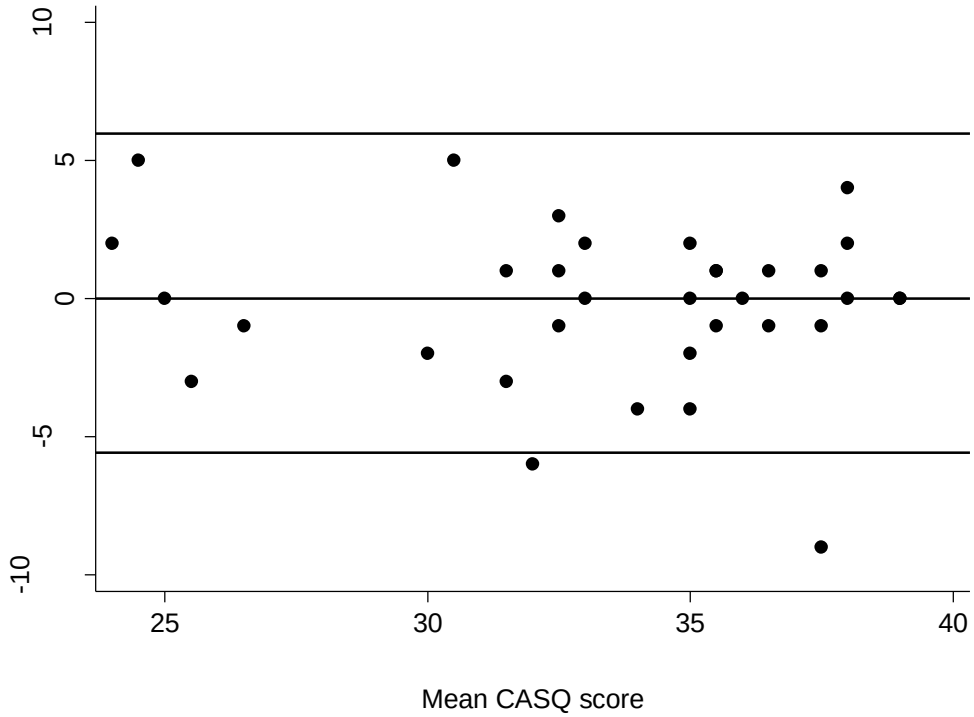

Figure 4.2: Bland-Altman plot to show the extent of the agreement between the total CASQ scores at time point one and time point two. The limits of agreement are included and demonstrate that 95% of the differences fall between these parameters.

4.2.4.3 Kappa coefficient

In order to measure the level of agreement of the CASQ scores, for each of the12 items in the instrument, between the two time points, the un-weighted and weighted Cohen's kappa coefficients were calculated (Table 4.3). Rather than simply calculating the percentage agreement between the two scores, the kappa coefficient takes into account the level of agreement that can occur by chance. A kappa value of one would indicate perfect agreement between the two scores, whereas a value of zero would indicate no agreement more than chance alone. A negative value would imply a level of agreement worse than chance. Table 4.4 shows the suggested levels of agreement attached to kappa by Landis and Koch (1977).

Table 4.3: Weighted and un-weighted kappa scores for each of the 12 items of CASQ

Question number	Question theme	Un-weighted kappa	Weighted kappa
5	Number of meals	1.00	1.00
2	Satiety	0.75	0.82
10	Mood	0.67	0.74
7	Taste compared with pre-illness	0.64	0.74
8	Taste changes	0.60	0.68
6	Number of snacks	0.52	0.63
11	Energy level	0.58	0.59
12	Pain	0.56	0.54
3	Hunger	0.46	0.54
4	Enjoyment of food	0.42	0.53
9	Nausea	0.41	0.53
1	Appetite	0.37	0.51

For each of the 12 items of the CASQ, the un-weighted and weighted kappa scores are shown.

Table 4.4:Suggested levels of agreement for values of kappa

Value of kappa	Strength of agreement
< 0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
0.80 -1.00	Very good

The suggested levels of agreement for values of kappa, as suggested by Landis and Koch (1977) are shown.

Taking these suggested values into consideration, all 12 items of the CASQ had weighted kappa values above 0.5. This implies that there was moderate to very

good agreement between the CASQ scores produced at the two time points.

4.2.4.4 Intraclass correlation coefficient

The intraclass correlation coefficient (ICC) is a ratio of the variance between subjects to the total variability, where total variability is the sum of between subject variability and measurement error, or 'within subject' variance. A value of one would imply that there was no measurement error, a 'perfect instrument'. For the CASQ the ICC was calculated as 0.80 (95% CI = 0.68 to 0.92).

4.3 Discussion

4.3.1 Study design

The key objective for Phase I of the study was to derive an estimate of the reliability of the CASQ. Indeed, reliability testing is an important step in the development of any new instrument which is to be used within the healthcare setting. Yet, reliability is not necessarily something that is easy to determine and the varied terminology within the literature often leads to confusion when interpreting reliability statistics.

An area of much debate, when determining the test-retest reliability of an instrument, is how long the time interval should be between administrations of the instrument. If it is too long there is a risk that the characteristics of the sample may have changed. Too short an interval may result in a memory effect and subjects will remember their previous responses. A study by Marx *et al*. (2003), comparing test-retest reliability (ICC and limits of agreement) of a health related quality of life instrument, at two days and two weeks, found no statistical differences over the two time intervals. This concurs with the suggestion from Streiner and Norman (2008) who suggest the retest interval should be between two and fourteen days. In this study the time interval between participants completing the CASQ was one week. As there is no agreed retest period it can be assumed that this is appropriate. There is however the possibility that completing the questionnaire at time point one made the participants more aware of their appetite and symptoms. This could have influenced their subsequent responses and indeed the estimated reliability of the instrument.

4.3.2 Study population

It is intended that the CASQ will be used with people who have got cancer and it is within this population that the reliability study was conducted. The sample tested in this study included similar numbers of males and females. It was also diverse in

terms of age and diagnosis. This is important as if the population tested is vastly different to the one that the instrument is intended to be used with one could argue that the estimated reliability may not be valid (Streiner and Norman, 2008). When determining test-retest reliability of an instrument, not only is the time frame over which the test takes place important, so is the stability of the sample. Testing the instrument on a population which has a rapidly changing clinical status, for example patients having chemotherapy, could lead to a dramatic change in appetite and symptoms over the course of even a few days. As patients in this study were receiving adjuvant rather than palliative radiotherapy, and those receiving treatment to the head, neck or upper gastrointestinal tract area or with a condition impairing their ability to swallow were excluded, it can be argued that the sample was clinically stable. In addition, all participants had a good performance status (ECOG 0/1) indicating that they were independent and overall able to perform all activities of daily living. What must be questioned is if the sample population is similar enough to the population where the CASQ will ultimately be used. From the results, there was certainly a difference in the variance of responses that the sample gave compared with what you would expect to see in a 'healthy population'. This can be seen from the large range (22 to 42) of total CASQ scores. This indicates that some subjects had an impaired appetite and presence of symptoms and is likely to be similar to the wider cancer population. However, it is possible that a sample taken from another group of patients, for example those undergoing chemotherapy or who have had recent surgery, would yield different results. In these groups CASQ scores may overall be lower and, if many of the patients were experiencing similar problems, the variance narrower. When developing a new instrument, practically it would be extremely time consuming to have to re-evaluate its reliability in a number of different patient groups. Plus, the clinical instability within such groups, between even the shortest time points, may lead to unreliable results. For these reasons testing the reliability of the CASQ in a wider and probably unstable cancer population would have been unsound, thus suggesting that the sample selection used in this study was likely to be the best possible.

4.3.3 Internal consistency

Based on the correlation between responses to items in the CASQ using the Cronbach's alpha coefficient, the internal consistency of the instrument was assessed (Cronbach, 1951). It is generally stated that the closer the resulting value is to one, the stronger the correlation and the higher the reliability. However, there is a lack of agreement in the literature as to what constitutes an acceptable level.

There is a body of evidence that suggests the acceptable value should be dependent on whether the instrument being tested is to be used as a research tool or in clinical practice (Bland and Altman, 1997; Charter, 2008). If the aim is the latter then the necessary level of acceptability is higher as it is more important to determine the population reliability. Others take the approach that the acceptable level is dependent also on the sample size (Ponterotto and Ruckdeschel, 2007). Streiner and Norman (2008) summarise that a value higher than 0.7 and lower than 0.9 is ideal. A very high Cronbach's alpha value, i.e. greater than 0.9, may simply be reflecting a large number of items being tested or suggesting that some of the items may be repetition of information and therefore unnecessary.

When looking at the internal consistency of the CASQ over all 12 items, the results were similar at time point one (0.76) and time point two (0.74). This result can be interpreted as there being an acceptable average reliability between the 12 items of the CASQ, with approximately 70% of the measured variability being reliable and 30% down to random error. As a research or clinical instrument, 0.7 has been proposed as the absolute minimum internal consistency reliability of test scores (Charter, 2008). This provides evidence to support the use of the CASQ in research or clinical practice. However, the 95% confidence intervals indicate that the true value could be as low as 0.6 or as high as 0.85 and this must be considered when interpreting the results.

Similar Cronbach's alpha values were achieved when looking at appetite specific (0.72 at time point 1 and 0.82 at time point 2) and symptom specific (0.65 at time point 1 and 0.72 at time point 2) items. Other areas of the CASQ appeared to be less well correlated. Items five and six both focus on level of food intake; meals and snacks. Generally some level of agreement between responses to these items would be expected. However, at both time points these items were negatively correlated (-0.40 and – 0.18 respectively). This negative value is possibly due to the ordering and response options available. Three meals a day is the standard meal pattern within the U.K. For items five and six to be correlated, subjects would also need to have three snacks a day. This may be unlikely in this particular population. Response options may also account for poor correlations between other questions. For example, when responding to item seven, subjects who thought food tasted 'just as good' were likely to respond to question eight with 'no changes in taste'. This would have resulted in a poor correlation between these items. Of course another reason for lower Cronbach's alpha values, and indeed the negative value, is that

there are only two items being tested. The more items in a scale the less random error matters as it will cancel itself out, resulting in a larger Cronbach's alpha value (Streiner and Norman, 2008). Interestingly, when each item was removed from the CASQ, one by one, the value never dropped below 0.7. This suggests that none of the individual items significantly reduced reliability. However, removing items five and six did increase the Cronbach's alpha value at both time points (0.8 and 0.78).

4.3.3.1 Unidimensionality

Within the literature, the Cronbach's alpha coefficient is often quoted as a measure of unidimensionality, or the extent to which all items within an instrument are measuring the same concept or dimension. However, there is debate as to the appropriateness of using Cronbach's alpha as a measure of unidimensionality of an instrument as the coefficient accounts for only a low limit of variance attributable to common factors (Falissard, 1999; Sijtsma, 2009). Despite its limitations, the use of Cronbach's alpha as a measure of internal consistency continues to be recommended by experts (Streiner and Norman, 2008).

It is important to consider how important it is for the CASQ to have unidimensionality. The overall purpose of the CASQ is to determine a person's level of nutritional risk so that nutritional treatment can be initiated, where necessary, in a timely manner. It is not the intention to compare one person to another or draw conclusions in terms of severity of appetite or symptoms experienced by an individual. Nutritional risk is not a homogenous entity. There are several dimensions that can contribute towards a person's nutritional risk. Indeed the CASQ incorporates three such dimensions; items relating to appetite, food intake and symptoms. In addition, one of the objectives of this study was to propose a multi-dimensional screening instrument, encompassing all aspects of the cachexia syndrome, which will predict weight loss in people with cancer. Therefore, one must question the need for the CASQ, as a 12 item tool, to have proven unidimensionality. If in clinical practice the CASQ is only to be used as a screening instrument, why the individual is at nutritional risk is of low importance. Whether they have one severe symptom or several minor ones, or if indeed they are symptom free but have a poor appetite and intake due to other factors, they will be at nutritional risk and this is ultimately the issue which needs to be addressed.

One way of determining if indeed the CASQ is composed of different dimensions would be to use factor analysis. However, it is possible that using this technique

would result in an instrument with reduced content validity and with key clinical questions made redundant. Instead, as suggested by Kessler and Mroczek (1995), multiple logistic regression was used in Phase II of the study to explore the optimum combination of items to include in the screening instrument.

4.3.4 Test-retest reliability: Measurement of agreement

Test-retest reliability is used to determine the consistency of a measure from one time point to another. In this study, it is the reproducibility of the CASQ scores between two time points one week apart, when administered to the same population, which was determined. To minimise contamination by external factors, the CASQ was administered within the same setting. To ensure a stable population, all subjects who documented an event during the previous week that had impacted on their appetite and/or symptoms, were excluded from this analysis.

4.3.4.1 Correlations

As can be seen from the scatter plot (Figure 4.1), there was a strong positive correlation between the total CASQ scores at the two time points, with minimal variation from the line of regularity. The Pearson correlation coefficient ($r = 0.80$, $P < 0.01$) also supports this finding. However, the correlation coefficient is a measure of the relationship between two items, not the level of agreement and therefore must be interpreted with caution. In addition, when testing the significance of the result, the null hypothesis is that the CASQ scores at time point one and time point two are not linearly related. It would be surprising if at the repeat administration of the CASQ, in a stable population, the responses were not related to those given initially.

4.3.4.2 Bland-Altman plot

To demonstrate more clearly the size of the differences between the total CASQ scores at the two time points and the scatter around zero, the results were plotted on a Bland-Altman plot. The Bland-Altman Plot (Figure 4.2) shows several important and positive points when considering the reliability of the CASQ. Firstly, 95% of the measurements fell within the limits of agreement (-5.90 to 5.92) demonstrating a normal distribution of the data (Bland and Altman, 1986). If the CASQ was administered to a new individual on two occasions we would expect the difference in their scores to be less than 5 in either direction. Secondly there was a random scatter of measurements around the point of zero. This is a positive result as it demonstrates that the size of the difference is not related to where participants were ranked in terms of appetite and symptoms. Finally, as the confidence interval for the

mean difference included zero, this suggests that there is no evidence of bias, i.e. total CASQ scores do not have a tendency to drift up or down.

4.3.4.3 Kappa coefficient

Simply calculating the proportion of participants giving the same answer to each question on the CASQ at time point one and time point two, would not take into account how the results were influenced by chance. For this reason the kappa coefficient for each of the 12 items of the CASQ can be calculated. The kappa coefficient gives a chance-corrected agreement. However, when the un-weighted kappa coefficient is calculated, there is no consideration for the extent of disagreement and values are likely to be lower. For this reason, as the data is ordinal, calculating the weighted kappa coefficient is favoured (Cohen, 1968). In this case, to calculate weighted kappa, responses to the 12 items of the CASQ, as described by Altman (1991), were given linear weightings of 1.0, 0.75, 0.5, 0.25 and 0 depending on their distance from the diagonal that indicates agreement. For the 12 individual items, values for weighted kappa ranged from 0.51 to 1.0. Several authors have proposed cut-off values for interpreting the kappa value (Fleiss and Cohen, 1973; Landis and Koch 1977), suggesting that the values obtained in this study indicate moderate to very good agreement between the two time points. Streiner and Norman (2008) however suggest that any value less than 0.6 should be disregarded as having an unacceptably low level of agreement. This would mean that six items in the CASQ have a questionable level of reliability. One possible reason for these lower values could be due to a real variation in subject's appetite and symptoms over the course of the week. Questions which had strong agreement asked about, for example, the number of meals or snacks eaten or changes in taste. These are all likely to be more stable variables over the course of one week.

4.3.4.4 Intraclass correlation coefficient

An intraclass correlation coefficient of 0.80 (95%CI = 0.68 to 0.92) suggests that 80% of the total variability is between subjects rather than within total CASQ scores at the two time points. This demonstrates good reliability of the CASQ as the measurement error, or difference between the CASQ scores at the two time points, is low.

4.3.5 Reliability of other nutrition screening instruments

Due to the way that reliability statistics are reported in the literature, comparison between screening instruments is not always possible. In addition, when there are

differences in the number of categories within items, and indeed the number of items in the instrument, comparisons need to be made with caution (Altman, 1991). Often, authors do not provide sufficient evidence to show how the reliability of their instrument has been determined, with many describing only the inter-rater reliability of the instrument (Detsky *et al*., 1987; Ferguson *et al*., 1999; Burden *et al*., 2001; Jones, 2002; Weekes *et al*., 2004). As the CASQ is self-reported, inter-rater reliability has not been established in this study and so cannot be compared. Few papers report the internal consistency or ICC of their instrument. The eight item Council on Nutrition Appetite Questionnaire (CNAQ), from which the CASQ was derived, has an estimated Cronbach's alpha value of 0.47 in a group of subjects in long-term care, and of 0.72 in community-dwellers (Wilson *et al*., 2005). The results from the CASQ analysis are similar in strength to those found by Wilson and colleagues (2005). However, the difference in the number of items in the two instruments should be considered. The ICC of the CNAQ was not reported so this cannot be compared. The Mini Nutritional Assessment (MNA) is an instrument that was developed to identify elderly patients who are malnourished (Vellas *et al*., 1999). Reliability testing of the MNA suggests an ICC of 0.89 (confidence intervals not reported) and Cronbach's alpha value of 0.74 (Bleda *et al*., 2002). These results are not too dissimilar to those estimated for the CASQ, suggesting that this level of reliability is acceptable when comparing it to other more established tools.

4.4 Conclusion

Reliability cannot be calculated. However, by using a combination of methods, giving consideration to the strengths and weakness of each, reliability can be estimated. In this study, two classes of reliability estimates have be used; internal consistency and test-retest reliability. The results suggest that within the test population, the CASQ scores had good test-retest reliability, and the 12 items show an acceptable degree of internal consistency. Phase II will determine the validity of the CASQ to predict weight loss in people with cancer.

CHAPTER 5: PHASE II: VALIDITY TESTING OF THE CANCER APPETITE AND SYMPTOM QUESIONNAIRE

5.1 Introduction

Many people experience a degree of weight loss prior to being diagnosed with cancer. Upon diagnosis some patients will present with the symptoms of the cachexia syndrome and malnutrition. Existing nutrition screening instruments, such as the Patient Generated Subjective Global Assessment (PG-SGA) and Malnutrition Screening Tool (MST), have been validated in people with cancer to identify those who are already exhibiting signs of malnutrition (Bauer *et al*., 2002; Isenring *et al*., 2006). In addition, some instruments, for example the Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment (MNA) and Nutritional Risk Screening 2002 (NRS-2002), when used in a hospital population, have proven predictive validity in terms of length of stay, clinical outcome and morbidity (Bauer *et al*., 2005; Kyle *et al*., 2006; Stratton *et al*., 2006). However, no tool, when tested with people who have cancer, appears to be predictive of weight loss. A screening instrument that can predict those people who are not already malnourished but who are likely to lose weight in the future may help to target nutritional advice and treatment in a proactive manner.

The key objectives for Phase II of the study were to:

9. Obtain an estimate of the reliability of the CASQ.
10. Determine the predictive validity of the CASQ
11. Determine the optimal cut points and overall performance of the CASQ at predicting clinically significant weight loss over three months.
12. Propose an optimum screening instrument to predict clinically significant weight loss over three months.

A longitudinal observational study with two test points, three months apart was used to meet these objectives. The study sample included patients with lung or upper GI cancer who were not at high risk of malnutrition. Self-completed CASQ scores, anthropometric data and serum concentrations of C-Reactive Protein (CRP) and albumin were collected and analysed. To estimate the predictive validity of the CASQ, correlations were calculated. Receiver Operating Characteristic (ROC) curve analysis was used to determine the optimal cut point, sensitivity and specificity of the instrument. To explore the optimum set of variables that could be included in a screening instrument to predict weight loss, multiple linear regression techniques

were used. Finally a Cox's regression survival analysis was performed to determine the ability of the CASQ, and other measured variables, to predict survival. The results of the analysis of the Phase II study data are presented in the subsequent section of this chapter. What follows is a discussion of the results, specifically focusing on the use of the CASQ as a predictor of weight loss in the cancer population.

5.2 Results

5.2.1 Phase II participant recruitment

In all, 346 subjects diagnosed with lung or upper GI cancer were approached and asked if they agreed to be screened for risk of malnutrition using the MUST. As demonstrated by the flow chart (Figure 5.1), only a small number (nine) declined the initial screening process. Of the remaining 337, 70% (236) met the study inclusion criteria of having a MUST score of less than two. Of those screened, 22% had no further involvement in the study. Whereas 16 patients failed to meet the other inclusion criteria for the study, 35 declined to take part. Anecdotally, reasons most frequently given for not wanting to take part were the burden of having to read through the participant information sheet or, not having their spectacles available. Some reported having "too much on" at the moment. Of the 16 that did not meet the inclusion criteria, one patient had ascites, one dementia and in two cases the primary cancer site had not been determined. The remaining 12 patients were excluded as the researcher deemed their inclusion inappropriate at that point in time. This was due to the patient being too unwell, receiving bad news or already currently participating in another research study. A total of 185 patients gave consent to take part. With a lower than expected attrition rate of 10%, this meant that 167 completed the three month study.

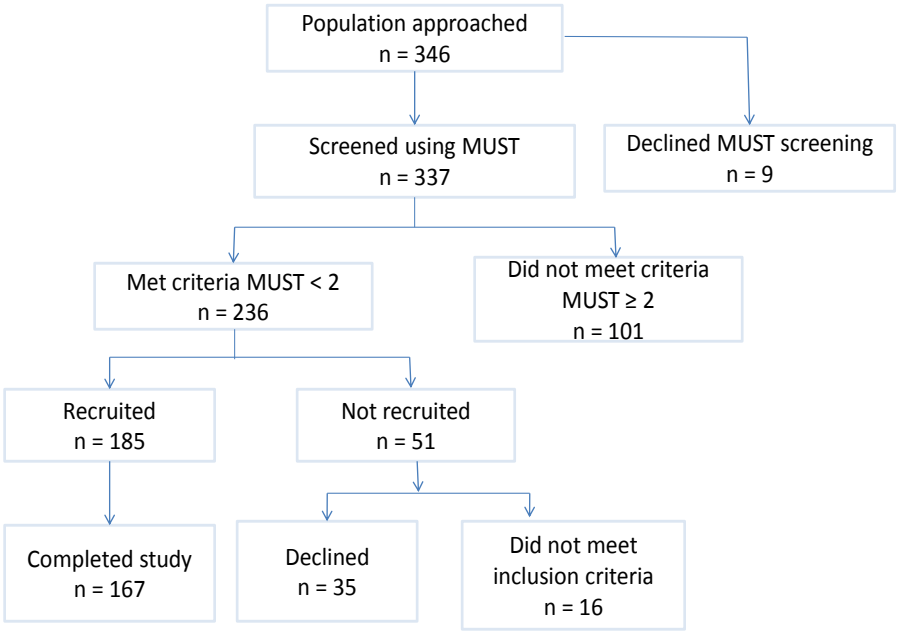

Figure 5.1: Flow chart of Phase II study population. The number of patients who were approached and asked to take part in the study, along with the number who were screened and finally recruited is shown.

5.2.2 Baseline characteristics of Phase II study population

The baseline characteristics of the 185 patients consented to take part can be seen in Table 5.1. Sixty-one percent of the study sample was male and the mean (SD) age was 66.7 (9.4) years. The majority (99.5%) of the population were white British. Ninety percent of the group had an ECOG performance status of zero or one. This suggests that the majority were independent and able to carry out all but the most strenuous activities of daily living. There was a reasonable split of participants between the two tumour groups, with 59% having a cancer of the upper gastrointestinal tract and 41% being diagnosed with lung cancer. The length of time since diagnosis ranged from less than one month to over five years (mean (SD) = 7.9 (9.6) months). The majority of patients (68%) were undergoing chemotherapy at some stage during the study period. For most of the study population the intent of their treatment was palliative, thus indicating that 72% had incurable disease.

Table 5.1: Baseline characteristics of Phase II study sample (n=185)

	Mean (SD)	Range	Missing (n)
Age (years)	66.7 (9.4)	42.9 to 86.7	0
Time since diagnosis (months)	7.9 (9.6)	0.2 to 63.3	0
Weight (kg)	74.4 (14.3)	44.2 to 121.2	1
Body Mass Index (kg/m^2)	26.0 (4.0)	18.8 to 41.5	1
% 3 to 6 months weight change	-0.3 (5.6)	-9.8 to 25.9	2
	n (%)		
Sex			0
Male	113 (61.1)		
Female	72 (38.9)		
Ethnicity			0
White British	184 (99.5)		
Other	1 (0.5)		
Social circumstances			1
Lives with partner	142 (76.8)		
Lives alone	34 (18.4)		
Lives with son or daughter	6 (3.2)		
Lives with other	2 (1.1)		
East Coast Oncology Group performance status			0
0-1	167 (90.1)		
>1	18 (9.7)		
Tumour group			0
Upper gastrointestinal	109 (58.9)		
Lung	76 (41.1)		
Primary tumour site			0
Pancreas	51 (27.6)		
Gastro-oesophageal	43 (23.2)		
Cholangiocarcinoma	12 (6.5)		
Liver	3 (1.6)		
Non small cell lung cancer	46 (24.9)		
Small cell lung cancer	26 (14.1)		
Mesothelioma	4 (2.2)		
Treatment intent			0
Curative	52 (28.1)		
Palliative	133 (71.9)		
Treatment during study			0
Chemotherapy	115 (62.2)		
Chemotherapy and surgery	3 (1.6)		
Chemotherapy and radiotherapy	2 (1.1)		
Radiotherapy	7 (3.8)		
Supportive care	58 (31.4)		

Baseline demographic, anthropometric and clinical details are shown. For the age and time since diagnosis, and the anthropometric measurements, the mean, standard deviation and range is given. Remaining results are shown as frequencies. The numbers of missing cases are also highlighted.

5.2.3 Baseline nutritional screening

As shown in Table 5.1, at baseline, the mean (SD) body weight and BMI of the study population was 74.4 (14.3) kg and 26 (4.0) kg/m^2 respectively. Table 5.2 shows additional baseline nutritional screening characteristics, including the categorisation according to BMI and percentage weight change of participants. Due to the exclusion criteria those with a MUST score greater than or equal to two, indicated by a BMI less than 18kg/m^2 or percentage weight change greater than ten percent, were excluded from taking part. The majority of participants (78%) had a MUST score of zero, with the remainder scoring one, indicating a moderate risk of malnutrition. Information collected also enabled the completion of an alternative screening instrument, the Malnutrition Screening Tool (MST) (Appendix 9). In contradiction to the MUST, a significant proportion of subjects were classified by the MST as being at high and medium risk of malnutrition, 28% and 21% respectively. Blood biochemistry monitoring showed that 53 participants had serum C-Reactive Protein concentrations greater than 10mg/L, which may be indicative of a systemic inflammatory response. One in five patients had an albumin level which was below the lower limit of normality. All participants were asked to provide a blood sample. As this frequently meant waiting for the clinic phlebotomist following their consultation with the doctor, compliance with this part of the study was poor. This resulted in the higher number of missing cases.

5.2.4 Cancer Appetite and Symptom Questionnaire responses

One hundred and eighty-one subjects completed the CASQ at baseline. Potential scores were zero to 48, with higher scores indicating fewer appetite and symptom problems. The mean score (SD) was 30 (6.5) and scores ranged from five to 45. The overall frequency of responses is shown in Table 5.3 and the percentage distribution in Figure 5.2. In total, 21% of respondents rated their appetite as poor or very poor. Most prominent symptoms potentially contributing towards a poor appetite included moderate or severe taste changes, and pain, reported by 33% and 27% of subjects respectively. In addition, just less than half (42%) of people reported never feeling sick or nauseated before eating. The majority of participants ate three meals (57%) and one or two (69%) snacks a day.

Table 5.2: Baseline nutrition screening characteristics of Phase II study population (n=185)

	Frequency (%)	Missing (n)
Body Mass Index (kg/m^2)		1
<18.5	0 (0)	
18.5 to 20	4 (2.2)	
20 to 25	78 (42.4)	
25 to 30	72 (39.1)	
30 to 35	27 (14.7)	
>35	3 (1.6)	
Weight change over previous 3 months (%)		2
+>10	8 (4.4)	
+5 to10	19 (10.4)	
0 to +5	57 (31.1)	
0 to -5	61 (33.3)	
-5 to10	38 (20.8)	
- >10	0 (0)	
Malnutrition Universal Screening Tool score		2
0	142 (77.6)	
1	41 (22.4)	
≥2	0 (0)	
Malnutrition Screening Tool score		
0	94 (51.1)	1
1	38 (20.7)	
≥2	52 (28.3)	
C-Reactive Protein (mg/L)		40
<5	72 (49.7)	
5 to 10	20 (13.8)	
≥10	53 (36.6)	
Albumin (g/L)		49
<30	29 (21.3)	
30 to 50	107 (78.7)	
>50	0 (0)	

Measured at baseline, the number of participants in each category of BMI, percentage weight change, MUST and MST scores are shown as frequencies. In addition, the C-Reactive Protein and albumin results are included. The numbers of missing cases are also highlighted.

Table 5.3: CASQ responses of Phase II study population at baseline (n=181)

	n (%)		n (%)
Q1. My appetite is…		Q2.When I eat I feel full…	
Very poor	8 (4.3)	Without having eaten anything	2 (1.1)
Poor	31 (16.8)	After eating only a few mouthfuls	16 (8.6)
Average	49 (26.5)	After eating about a third of a meal	19 (10.3)
Good	58 (31.4)	After eating over half of a meal	64 (34.6)
Very good	39 (21.1)	After eating a full meal	84 (45.4)
Q3.Before eating I feel hungry…		Q4.I enjoy the food I eat…	
Rarely	18 (9.7)	Most times	115 (62.2)
Occasionally	31 (16.8)	Often	21 (11.4)
Some of the time	71 (38.4)	Sometimes	39 (21.1)
Most of the time	54 (29.2)	Rarely	7 (3.8)
All of the time	11 (5.9)	Never	3 (1.6)
Q5. At present I eat…		Q6. At present I eat (in addition to or instead of a meal)…	
Less than one meal a day	3 (1.6)	No snacks	37 (20.0)
One meal a day	15 (8.1)	One snack a day	67 (36.2)
Two meals a day	50 (27.0)	Two snacks a day	61 (33.0)
Three meals a day	105 (56.8)	Three snacks a day	16 (8.6)
More than three meals a day	11 (5.9)	Four or more snacks a day	3 (1.6)
Q7. Compared to before I was ill, food tastes…		Q8. At present I have…	
Much worse	15 (8.1)	No changes in taste	76 (41.1)
Worse	55 (29.7)	Mild taste changes	43 (23.2)
Just as good	100 (54.1)	Moderate taste changes	48 (25.9)
Better	9 (4.9)	Severe taste changes	14 (7.5)
Much better	6 (3.2)	No taste at all	4 (2.2)
Q.9 I feel sick or nauseated before I eat or when I eat…		Q10. Most of the time my mood is…	
Most times	5 (2.7)	Very sad	3 (1.6)
Often	4 (2.2)	Sad	7 (3.8)
Sometimes	48 (25.9)	Neither sad nor happy	84 (45.4)
Rarely	50 (27.0)	Happy	75 (40.5)
Never	78 (42.2)	Very happy	15 (8.1)
Q11.Most of the time my energy level is…		Q12. Most of the time my pain is…	
Very high	2 (1.1)	Very mild or no pain	108 (58.4)
High	27 (14.6)	Mild	26 (14.1)
Moderate	91 (49.2)	Moderate	41 (22.2)
Low	53 (28.6)	Severe	1 (0.5)
Very low	12 (6.5)	Very severe	9 (4.9)

The frequency of the responses given to the 12 items on the CASQ are shown.

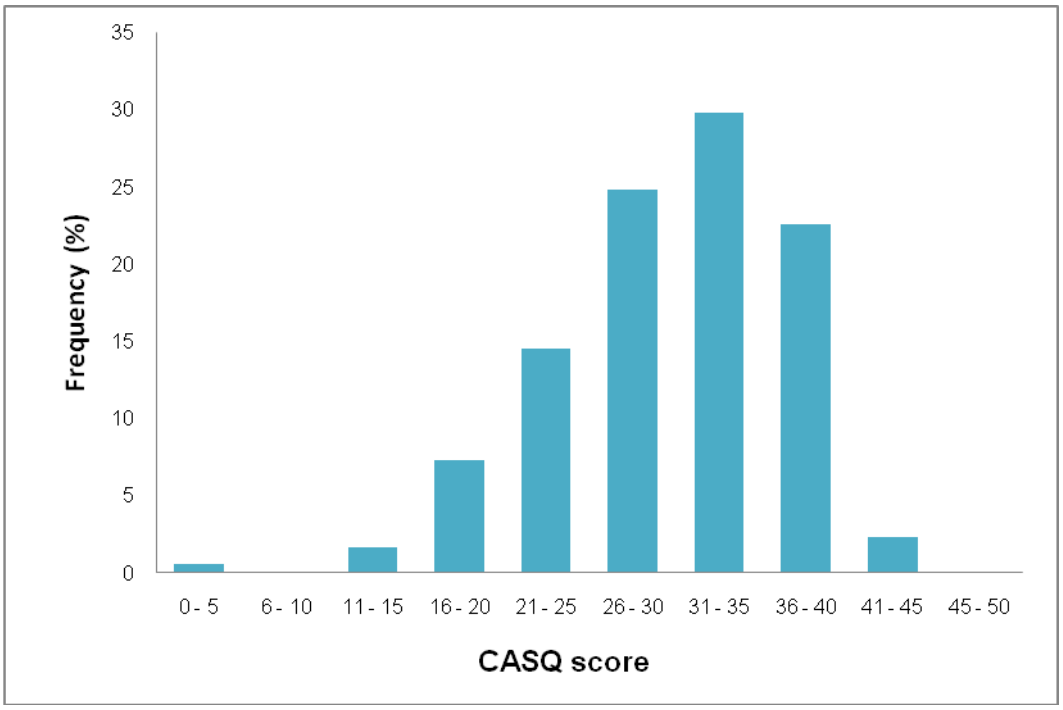

Figure 5.2: Percentage frequency distribution of total CASQ scores given by the 181 respondents.

It is of interest to determine whether there was a difference in appetite and symptoms between participants with different tumour group diagnoses. Table 5.4 provides the responses from the lung and upper GI cancer groups. The mean score (SD) for the respondents with upper GI cancer (n=106) was 30 (7.3) and the range five to 42. For those with lung cancer (n=75) the mean score (SD) was also 30 (6.3), range 16 to 45. There was no statistical difference between the two groups in terms of total CASQ score (P = 0.61). Twenty-three percent of those with upper GI cancer reported a poor or very poor appetite, compared with 18% of those from the lung cancer group (not significant). Generally, frequency of responses was similar across the two groups. Differences were not statistically significant at the 5% level. There was however a noticeable difference in reported energy levels between the two groups, with 42% of those with lung cancer responding to the low or very low category compared with 30% of subjects with upper GI cancer (P=0.07).

Table 5.4: CASQ responses for upper GI and lung cancer groups at baseline

	Frequency (%) Upper GI	Lung		Frequency (%) Upper GI	Lung
Q1. My appetite is…			Q2.When I eat I feel full…		
Very poor	7(6.4)	1(1.3)	Without having eaten anything	0 (0)	2(2.6)
Poor	18(16.5)	13(17.1)	After eating only a few mouthfuls	14(12.8)	2(2.6)
Average	27(24.8)	22(28.9)	After eating about a third of a meal	12(11.0)	7(9.2)
Good	36(33.0)	22(28.9)	After eating over half of a meal	37(33.9)	27(35.5)
Very good	21(14.3)	18(23.7)	After eating a full meal	46(42.2)	38(50.0)
	P* = 0.51			P* = 0.15	
Q3.Before eating I feel hungry.			Q4.I enjoy the food I eat…		
Rarely	12(11.0)	6(7.9)	Most times	68(62.4)	47(61.8)
Occasionally	16(14.7)	15(19.7)	Often	9(8.3)	12(15.8)
Some of the time	43(39.4)	28(36.8)	Sometimes	25(22.9)	14(18.4)
Most of the time	33(30.3)	21(27.6)	Rarely	5(4.6)	2(2.6)
All of the time	5(4.6)	6(7.9)	Never	2(1.8)	1(1.3)
	P* = 0.87			P* = 0.74	
Q5. At present I eat…			Q6. At present I eat (in addition to or instead of meal)…		
Less than one meal a day	2(1.9)	1(1.3)	No snacks	19(17.6)	18(23.7)
One meal a day	9(8.3)	6(7.9)	One snack a day	43(39.8)	24(31.6)
Two meals a day	25(23.1)	25(32.9)	Two snacks a day	37(34.3)	24(31.6)
Three meals a day	68(63.0)	37(48.7)	Three snacks a day	8(7.4)	8(10.5)
More than three meals a day	4(3.7)	7(9.2)	Four or more snacks a day	1(0.9)	2(2.6)
	P* = 0.65			P* = 0.98	
Q7. Compared to before I was ill, food tastes…			Q8. At present I have…		
Much worse	12(11.0)	3(3.9)	No changes in taste	46(42.2)	30(39.5)
Worse	31(28.4)	24(31.6)	Mild taste changes	26(23.9)	17(32.4)
Just as good	60(55.0)	40(52.6)	Moderate taste changes	29(26.6)	19(25.0)
Better	3(2.8)	6(7.9)	Severe taste changes	7(6.4)	7(9.2)
Much better	3(2.8)	3(3.9)	No taste at all	1(0.9)	3(3.9)
	P* = 0.21			P* = 0.40	
Q.9 I feel sick or nauseated before I eat or when I eat…			Q10. Most of the time my mood is…		
Most times	4(3.7)	1(1.3)	Very sad	2(1.8)	1(1.3)
Often	3(2.8)	1(1.3)	Sad	5(4.6)	2(2.7)
Sometimes	34(31.2)	14(18.4)	Neither sad nor happy	47(43.1)	37(49.3)
Rarely	24(22.0)	26(34.2)	Happy	45(41.3)	30(40.0)
Never	44(40.4)	34(44.7)	Very happy	10(9.2)	5(6.7)
	P* = 0.11			P* = 0.68	
Q11.Most of the time my energy level is…			Q12. Most of the time my pain is…		
Very high	2(1.8)	0(0)	Very mild or no pain	58(53.2)	50(65.8)
High	19(17.4)	8(10.5)	Mild	20(18.3)	6(7.9)
Moderate	55(50.5)	36(47.4)	Moderate	24(22.0)	17(22.4)
Low	25(22.9)	28(36.8)	Severe	7(6.4)	3(3.9)
Very low	8(7.3)	4(5.3)	Very severe	0(0)	0(0)
	P* = 0.07			P* = 0.20	

*Mann Whitney U test

The frequency of the responses given to the 12 items on the CASQ, comparing those participants who had lung and upper GI cancer, are shown. The statistical significance of the differences between the results is demonstrated using the Mann Whitney U test

5.2.5 Follow-up status and characteristics

Three month follow-up data was obtained from 167 (90%) subjects (Table 5.5). Of those who did not complete the study, fourteen (8%) participants had died. It was not possible to collect body weight from four other people within the follow up period.

Table 5.5: Characteristics of Phase II study population at three month follow-up (n=185)

	Mean (SD)	Range	Missing (n)
Weight (kg)	73.2 (14.2)	42.2 to 116.0	18
Body Mass Index (kg/m^2)	25.6 (4.1)	18.8 to 40.8	18
% weight change over 3 month study *	-1.4 (6.2)	-25.8 to 13.6	18
	n (%)		
Body Mass Index (kg/m^2)			18
<18.5	0 (0)		
18.5 to 20	11 (6.6)		
20 to 25	76 (45.5)		
25 to 30	54 (32.3)		
30 to 35	24 (14.4)		
>35	2 (1.2)		
% weight change over 3 month study			18
+ >10	6 (3.6)		
+ 5 to 10	16 (9.6)		
+0 to 5	53 (31.7)		
- 0 to 5	54 (32.3)		
-5 to 10	20 (12.0)		
-> 10	18 (10.8)		
-> 10	18 (10.8)		

*Negative values indicate weight loss, positive values indicated weight gain

The mean, standard deviation and range for the anthropometric measurements that were recorded at the three month follow-up period are shown. The frequency of participants falling into BMI and percentage weight loss categories has also been presented.

The mean (SD) body weight of those reassessed at follow up was 73.2 (14.2) kg. Figure 5.3 shows the mean body weight of participants at baseline and at three month follow-up. When tested using a paired sample T-Test, this analysis suggests that there was a small (1.2 kg), but statistically significant, change in mean body weight in the cohort overall ($t = 2.91$, $P = 0.004$). The mean (SD) percentage weight change over the three month period was -1% (6). Percentage weight change ranged from a weight loss of 26% to a weight gain of 14%. Fifty-five percent of participants lost some weight during the study period and for almost half of this group (23%),

that weight loss was clinically significant, i.e. greater than five percent. In addition, as seen in Figure 5.4, there was a shift in BMI categorisation compared with baseline with more people falling into the underweight and healthy weight class than the overweight and obese categories. Analysing the change in BMI between the two time points, using the paired sample T-Test, suggests that this shift was statistically significant (t = 3.07, P = 0.003).

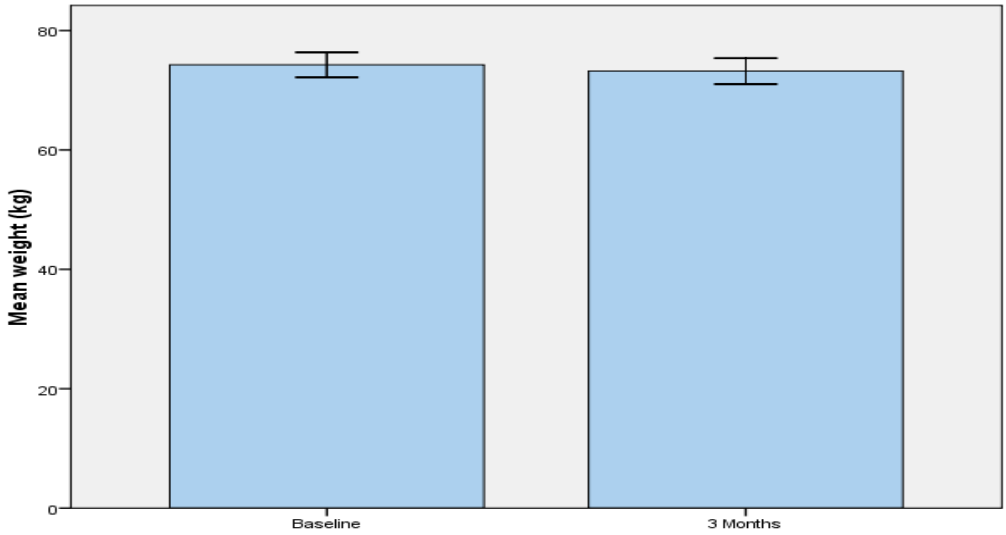

Figure 5.3: Mean weight of participants (with 95% confidence intervals) at baseline and three months. The mean difference from baseline to three months was -1.2kg where t = 2.91 (P = 0.004).

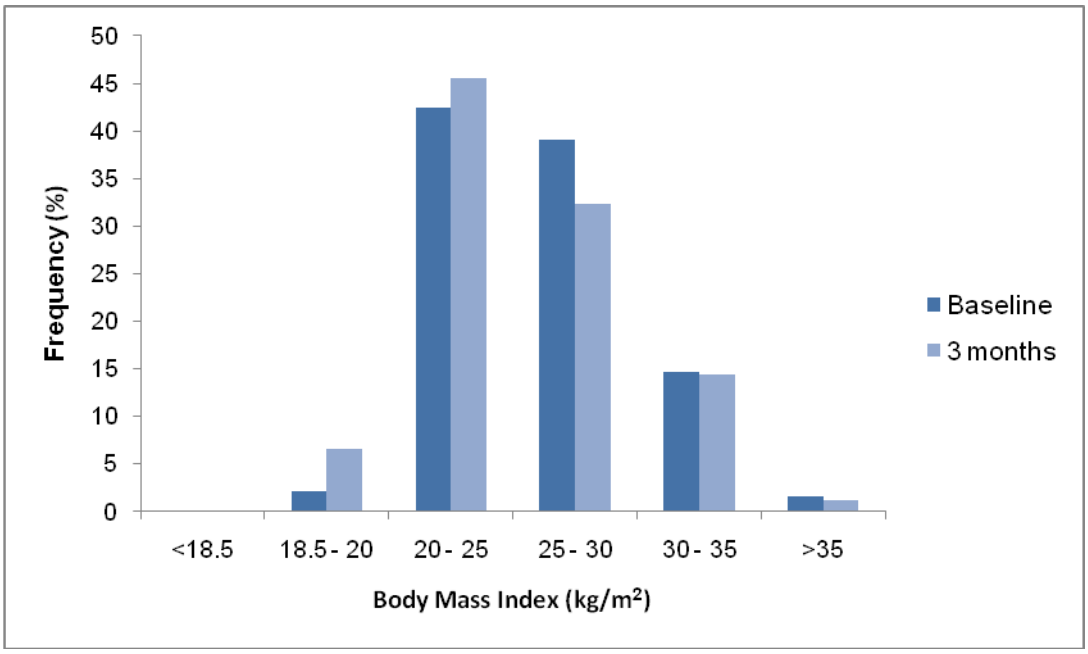

Figure 5.4: Percentage frequency distribution of participants' BMI at baseline and three month follow-up.

5.2.6 Predictive validity of the Cancer Appetite and Symptom Questionnaire

To determine the predictive validity of the CASQ, in terms of weight change at three months, the Pearson's correlation coefficient was determined. Figure 5.5 shows a positive correlation between the two variables, CASQ score at baseline and percentage weight change at three months, where r = 0.32 (P<0.001). The graphical representation also demonstrates that there were fewer participants with a very low total CASQ score.

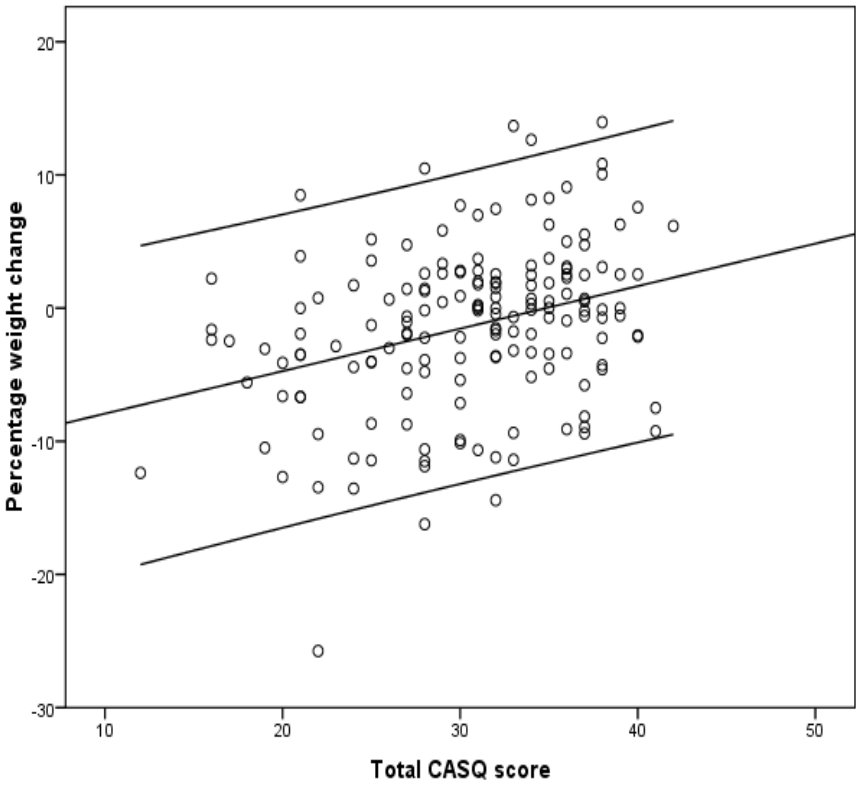

Figure 5.5: Correlation between total CASQ score at baseline and percentage weight change at three months. For this correlation r = 0.32 and P < 0.001. Trend line and 95% confidence intervals are plotted for these data.

To explore the association between total CASQ score and weight loss further, unadjusted linear regression was performed. This suggests that there was an estimated percentage weight gain of 0.3% (95%CI = 0.17 to 0.47) for every one unit increase in CASQ score (P<0.001).

The Spearman's coefficient was used to determine the correlation between the 12 individual items on the CASQ and weight change at three months (Table 5.6). All items were positively correlated with percentage weight change. That is to say, as

appetite and symptoms improved, percentage weight change was increased. For six of the items, items three, five, seven, eight, ten and eleven, the correlations were not statistically significant. Other items were shown to be more strongly correlated with percentage weight change. Values for items one, two, four, nine and twelve were statistically significant at the P=0.01 level and item six at the P=0.05 level.

Table 5.6: Correlation between item CASQ score at baseline and percentage weight change at three months

CASQ Item	Spearman rho (ρ)	P value	Missing (n)
2 (Satiety)	0.33	<0.001	18
1 (Appetite)	0.30	<0.001	18
4 (Enjoy food)	0.29	<0.001	18
9 (Nausea)	0.25	<0.01	19
12 (Pain)	0.24	<0.01	19
6 (Snacks)	0.18	0.02	18
10 (Mood)	0.13	0.11	19
3 (Hunger)	0.12	0.14	18
7 (Taste)	0.11	0.16	18
8 (Taste change)	0.10	0.21	19
5 (Meals)	0.01	0.26	19
11 (Energy)	0.03	0.67	18

For each of the 12 items in the CASQ, the score at baseline has been correlated with percentage weight change at three months. The Spearman's coefficients are shown, along with the P value and the number of missing cases. The items are ordered according to the strength of the correlation.

5.2.7 Other predictors of weight loss

Correlations were also used to determine the relationship between the additional measured variables and percentage weight change at three months (Table 5.7). The strongest correlation ($r = -0.34$, $P < 0.001$) was found with C-Reactive Protein and percentage weight loss (Figure 5.6). This indicates that as C-Reactive Protein concentrations rise, there is a tendency for percentage weight loss to increase. Interestingly, there was also a weak negative correlation between two previously validated nutrition screening instruments, the MUST and MST, and percentage weight change. Only the MST result was statistically significant. Baseline percentage weight change and percentage weight change at follow-up were also found to be positively correlated ($r = 0.22$, $P < 0.01$).

Table 5.7: Correlation between measured variables and percentage weight change at three months

Variable	Pearson coefficient (r)	P value	Missing (n)
C-Reactive Protein	-0.34	<0.001	53
Baseline % weight change	0.22	<0.01	19
Age	-0.17	0.03	18
Baseline BMI	-0.09	0.23	19
Albumin	0.01	0.92	62
Variable	Spearman rho (ρ)	P value	Missing (n)
MST score	-0.16	0.05	19
MUST score	-0.13	0.09	20
Performance status	-0.04	0.60	18

The correlation coefficients, Pearson's for parametric data and Spearman's for non parametric data, show the association between the measured variables and weight change at three month follow-up. The corresponding P value is also included, along with the number of missing cases.

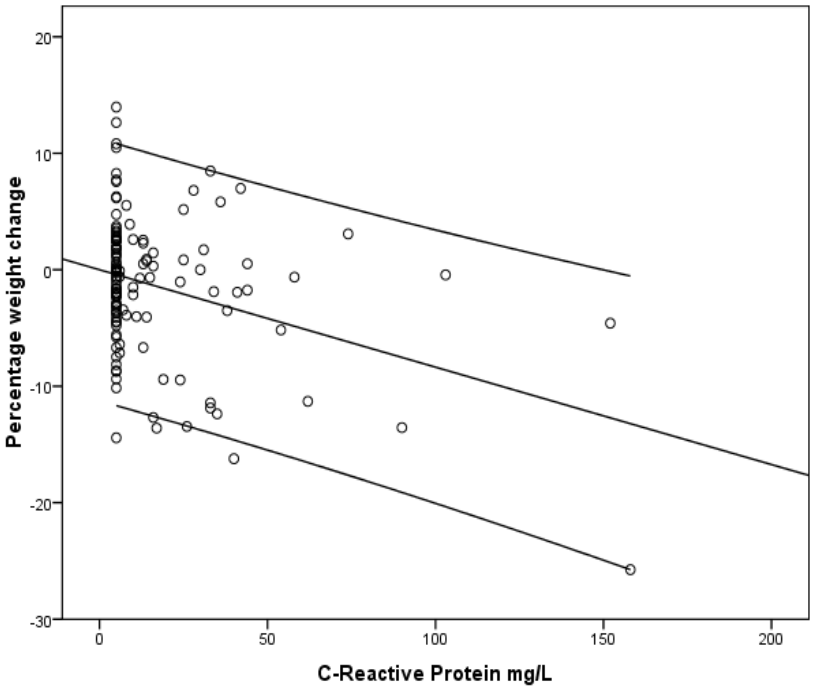

Figure 5.6: Correlation between C-Reactive Protein concentration at baseline and percentage weight change at three months. For this correlation r = -0.34 and P < 0.01. Trend line and 95% confidence intervals are plotted for these data.

To explore the association between C-Reactive Protein and weight loss further, unadjusted linear regression analysis was performed using dichotomous response variables of 0 = ≤10mg/L and 1 = >10mg/L (Table 5.8). This demonstrated that transition from a low C-Reactive Protein group (CRP ≤10mg/L) to a high C-Reactive Protein group (CRP >10mg/L) was associated with an estimated average percentage weight loss of 3% (95%CI -5.33 to -1.06, P < 0.01).

Table 5.8: Unadjusted linear regression analysis of C-Reactive Protein and percentage weight change

Predictor variable	Regression coefficient (B)	S.E.	95% confidence intervals	P value
C-Reactive Protein	-3.19	1.08	-5.33 to -1.06	<0.01

The results from unadjusted linear regression of C-Reactive Protein and percentage weight change are shown. For this regression, the regression coefficient (B) = -3.19 (95%CI -5.33 to -1.06, P <0.01).

To examine the association between percentage weight change of greater than 5% or 10%, and the categorical variables of treatment intent, diagnosis or gender, the Chi squared test was used (Table 5.9). Strong evidence of an association between diagnosis and percentage weight change was found. Just over one third (37%) of those diagnosed with gastro-oesophageal cancer lost more than 5% of their body weight during the study period. This was in comparison to 24% of those with pancreatic cancer. In addition, 12% and 16% of subjects with non small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) respectively experienced 5% weight loss or more (P=0.06). There did not appear to be any relationship between treatment intent and percentage weight change and only a weak, non-significant association with gender and 10% weight loss (P = 0.15).

Table 5.9: Association between percentage weight loss and treatment intent, diagnosis or gender

	>5% weight loss		>10% weight loss	
Variable	Chi ^{2}	P value	Chi^2	P value
Diagnosis	12.1	0.06	13.5	0.04
Gender	0.2	0.90	2.1	0.15
Treatment intent	0.1	0.80	0.8	0.40

Tested by the chi^2 coefficient and the corresponding P value, the association between percentage weight loss at the 5% and 10% levels, and the categorical variables of diagnosis, gender and treatment intent is shown.

5.2.8 The Cancer Appetite and Symptom Questionnaire as a screening instrument for weight change.

To determine the diagnostic performance of the CASQ as a screening instrument to predict weight change in people with cancer, Receiver Operating Characteristic (ROC) curve analysis was used (Altman and Bland, 1994). The analysis was performed at two levels to ascertain the performance of the CASQ at predicting 5% weight loss (Figure 5.7) and 10% weight loss (Figure 5.8). The ROC curve is determined by plotting the sensitivity against (1-specificity) for every possible cut point of the CASQ scores. Sensitivity is expressed as a proportion of the true positive rate. This is the percentage of patients who have greater than 5% weight loss and who have a positive test result, i.e. low CASQ score. Specificity is expressed as a proportion of the true negative rate. This is the percentage of patients who have not lost greater than 5% body weight and who have a negative test result, i.e. high CASQ score. A perfect instrument or test, with 100% sensitivity and 100% specificity would have an area under the ROC curve (C statistic) equal to one and the curve would pass through the left and top sides of the graph. In this study, the area under the curve represents the probability that a randomly chosen person who has lost 5 or 10% of their body weight during the study period will have a lower CASQ score than a randomly chosen person who has not lost 5 or 10% weight.

5.2.8.1 Test for 5% weight loss

The area under the ROC curve (C statistic) in Figure 5.7 was 0.64 (S.E. = 0.05, 95% CI 0.54 to 0.75, P <0.01). This means that if two people were selected at random from our sample, one who had lost more than 5% body weight and one who had not, the probability of the one who had lost more than 5% body weight having a low CASQ score would be 64%.

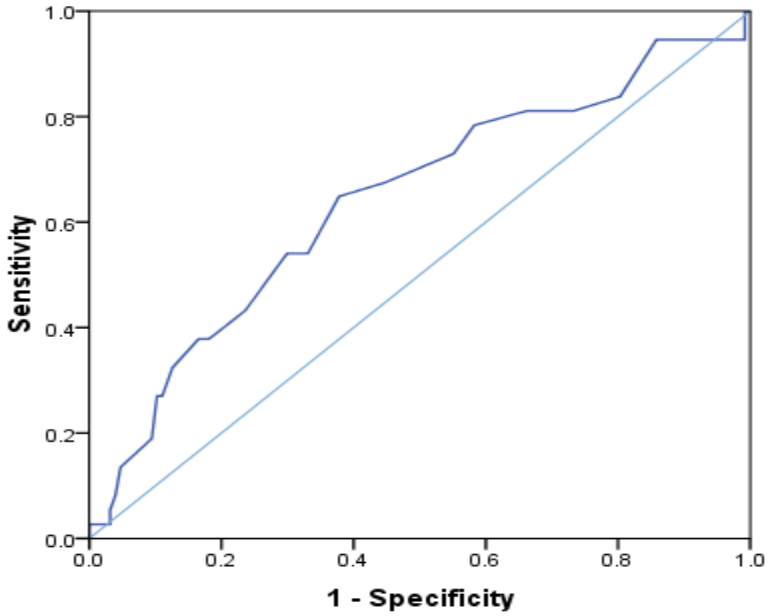

Figure 5.7: ROC curve for CASQ scores as a test for 5% weight loss. The ROC curve shows the sensitivity and specificity corresponding to different choices of cut-off points for CASQ scores as a test for 5% weight loss. Area under the curve = 0.64 (95%CI 0.54 to 0.75, P <0.01).

5.2.8.2 Determining the optimal cut point for the CASQ scores for predicting 5% weight loss

The level of sensitivity and specificity corresponding to each of the different cut points for the CASQ scores for 5% weight loss is shown in Table 5.10. The optimal cut point can be determined by taking the maximum sum of sensitivity and specificity, where the specificity/sensitivity is nearest to one (Altman and Bland, 1994). For predicting 5% weight loss this would mean the optimal cut point would be a CASQ score of 31 or less. To predict 5% weight loss, using a cut point of 31, the sensitivity of the CASQ was 65% and the specificity 62%. In addition, the positive predictive value (PPV), or proportion of patients with a positive test result, i.e. a low CASQ score, who were correctly identified as losing greater than 5% weight loss was 33%. The negative predictive value (NPV), or proportion of patients with a negative test result i.e. a high CASQ scores, who were correctly identified as not losing greater than 5% weight loss, was 86%.

Table 5.10: Sensitivity and specificity corresponding to different choices of cut-off points for CASQ score as a test for 5% weight loss

Cut Point	Sensitivity (%)	Specificity (%)	PPV(%)	NPV(%)	Specificity/Sensitivity
20	8.1	96.1	37.5	78.2	11.9
25	32.4	87.4	42.9	81.6	2.7
30	54.1	66.9	32.3	83.3	1.2
31	64.9	62.2	33.3	85.9	1.0
32	67.6	55.1	30.5	85.4	0.8
35	81.1	33.9	26.3	86.0	0.4
40	94.6	3.9	22.3	31.4	0.04

Calculated using ROC curve analysis for 5% weight loss, the sensitivity (Sn), specificity (Sp) and positive (PPV) and negative (NPV) predictive values are shown at seven cut-off points of total CASQ scores. The sensitivity divided by the specificity is also shown to demonstrate the optimal cut point which is where it is equal to one.

5.2.8.3 Test for 10% weight loss

For subjects with more than 10% weight loss the area under the ROC curve (C statistic) in Figure 5.8 was 0.75 (S.E. = 0.049, 95% CI 0.65 to 0.84, P = 0.001). As interpreted above, this means that if two people were selected at random from our sample, one who had lost more than 10% body weight and one who had not, the probability of the one who had lost more than 10% body weight having a low CASQ score would be 75%.

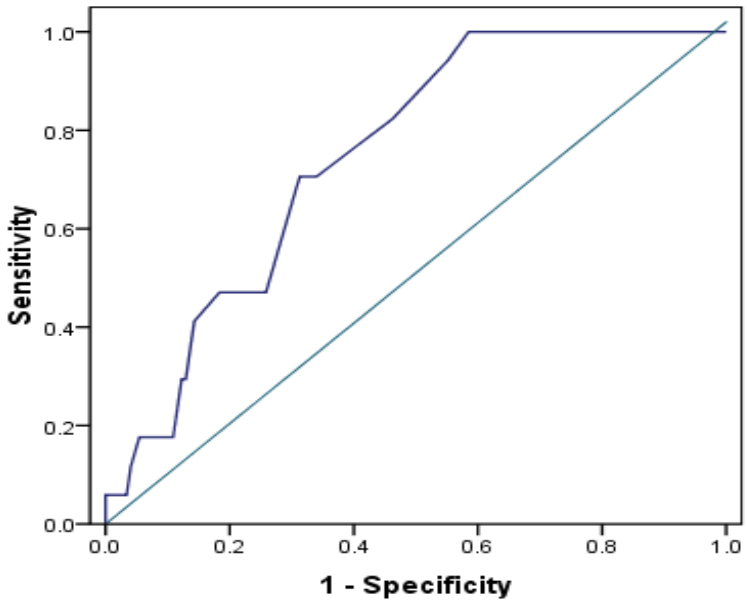

Figure 5.8: ROC curve for CASQ scores as a test for 10% weight loss. The ROC curve shows the sensitivity and specificity corresponding to different choices of cut-off points for CASQ scores as a test for 10% weight loss. Area under the curve = 0.75 (95%CI 0.65 to 0.84, P = 0.001).

5.2.8.4 Determining the optimal cut point for the CASQ scores for predicting 10% weight loss

The level of sensitivity and specificity corresponding to each of the different cut points for the CASQ scores for 10% weight loss is shown in Table 5.11. Using a cut point of 29 or less, to predict 10% weight loss, the sensitivity of the CASQ was 71% and the specificity 69%. The PPV and NPV were 21% and 95% respectively.

Table 5.11: Sensitivity and specificity corresponding to different choices of cut-off points for CASQ score as a test for 10% weight loss

Cut Point	Sensitivity (%)	Specificity (%)	PPV(%)	NPV(%)	Specificity/Sensitivity
20	11.8	95.5	25.0	90.4	8.2
25	41.2	85.7	25.0	92.6	2.1
28	47.1	74.1	17.4	92.4	1.6
29	70.6	68.7	20.7	95.3	1.0
30	70.6	66.0	19.4	95.1	0.9
35	100	34.0	14.9	100	0.3
40	100	4.8	10.8	100	0.1

Calculated using ROC curve analysis for 10% weight loss, the sensitivity (Sn), specificity (Sp) and positive (PPV) and negative (NPV) predictive values are shown at seven cut-off points of total CASQ scores. The sensitivity divided by the specificity is also shown to demonstrate the optimal cut point which is nearest to one.

5.2.9 Level of agreement between the CASQ and other screening instruments at identifying at risk patients

To determine the level of agreement between the CASQ and other existing screening instruments at identifying at risk patients, results were cross-tabulated and the proportion of agreement calculated (Table 5.12). As determined by the ROC curve and optimal cut point analysis for predicting 5% weight loss (described in section 5.2.8), patients with a total CASQ score of ≤ 31 were categorized as ‘at risk’. Those with a MUST score of one, a MST score of more than two or a C-Reactive Protein measurement of >10mg/L were also classified as ‘at risk’. When comparing the CASQ with the other screening instruments, the highest level of agreement was with the MST. The two instruments agreed in the classification of ‘at risk’ in 64% of cases. Overall, the MUST and MST had the highest level of agreement (88%) when identifying at risk patients.

Table 5.12: Proportion of agreement between screening instruments

	CASQ	MST	MUST	CRP
CASQ		64.1%	55.5%	53.9%
MST			88.0%	66.6%
MUST				66.4%

From cross-tabulation analysis, the percentage agreement between screening instruments, when identifying patients as 'at risk', is shown. For example, the MUST and CASQ only agreed in their classification of patients as 'at risk' in 55.5% of cases. For the remaining cases one of the instruments classified patients at risk, the other did not.

5.2.10 Comparison of the CASQ and other screening instruments as predictors of 10% weight loss

ROC curve analysis was used to establish how the CASQ performed when predicting 10% weight loss compared with the other screening instruments (Table 5.13). As discussed above, the area under the curve represents the probability that for a randomly chosen person who is a case, i.e. has lost 10% of their body weight during the study period, for C-Reactive Protein, the MUST and MST instruments, the results will be a high score, than for a randomly chosen person who is not a case. When measuring C-Reactive Protein, this means that if two people were selected at random from our sample, one who had lost more than 10% body weight and one who had not, the probability of the one who had lost more than 10% body weight having a raised C-Reactive Protein would be 80%.

The optimal cut point can be determined by taking the maximum sum of sensitivity and specificity, where the specificity/sensitivity is nearest to one. Table 5.13 shows the optimum cut point for the MUST and MST to be greater than or equal to one and two respectively. This corresponds with the cut points currently used in clinical practice. C-Reactive Protein analysis suggests that the optimum cut point is >15mg/L. At this level the sensitivity of the instrument is 83% and the specificity 81%. In addition, the positive predictive value (PPV), or proportion of patients with a high C-Reactive Protein who lost greater than 10% body weight, was 30%. The negative predictive value (NPV), or proportion of patients with low C-Reactive Protein who did not lose greater than 10% weight loss, was 98%.

For all instruments, the area under the curve was highest when predicting 10% weight loss when compared with 5% weight loss (CRP, C statistic = 0.65 95% CI = 0.52 to 0.77; MST, C statistic = 0.59 95%CI = 0.48 to 0.70; MUST, C statistic = 0.57 95%CI = 0.46 to 0.68).

5.13: Comparison of the sensitivity and specificity of the CASQ and other screening instruments when predicting 10% weight loss

Screening instrument	C statistic	S.E	95% Confidence Interval	P value	Cut point	Sn (%)	Sp (%)	PPV (%)	NPV (%)
CRP	0.80	0.08	0.66 to 0.95	<0.01	>10	83.3	70.0	21.7	97.7
					>15	83.3	80.8	30.0	98.0
CASQ	0.75	0.05	0.65 to 0.84	<0.01	≤29	70.6	68.7	20.7	95.3
MUST	0.67	0.07	0.52 to 0.81	0.02	≥1	50.0	83.0	26.5	93.1
MST	0.63	0.08	0.48 to 0.78	0.08	≥2	50.0	76.4	20.5	92.6

ROC curve analysis was performed for the four instruments to determine their ability to predict 10% weight loss. For each instrument, the area under the curve (C), with 95% confidence intervals and the corresponding P value are shown. Using the optimal cut points the sensitivity (Sn), specificity (Sp) and positive (PPV) and negative (NPV) predictive values are shown. For C-Reactive Protein, the cut point used in clinical practice is also included.

5.2.11 Exploratory modelling using multiple linear regression analysis

To build a model of the optimal set of variables that could comprise a screening instrument to predict weight change, multiple linear regression analysis was used. Two potential models were explored. The first model was fitted using the percentage weight change at follow up as the dependent variable, and the twelve items from the CASQ, plus the total CASQ score, as predictor variables. As a backward variable selection process was used initially, all 13 predictor variables were put into the model, at each step, the variable with the highest P value was dropped. Variables were retained where $P < 0.10$ for log-likelihood ratio tests. The resulting model (Table 5.14) consisted of three of the variables; CASQ item 6, relating to the amount of snacks eaten, CASQ item 9, concerning sickness and nausea and CASQ item 12 regarding level of pain. The predictive equation derived from the modelling process is as follows, where the constant regression coefficient is -17.68 and the relative predictive power of the model (r^2) equals 0.12:

% weight change = -17.68 + (CASQ item 6 score x 1.45) + (CASQ item 9 score x 1.14) + (CASQ item 12 score x 1.81)

The closer the r^2 value is to one, the greater the ability of the model to predict percentage weight change.

Table 5.14: Model 1 determined by multiple linear regression analysis using CASQ items and total score as predictor variables

Predictor variable	Regression coefficient (B)	S.E.	95% confidence intervals	P value
CASQ item 12	1.81	0.60	0.63 to 2.99	0.01
CASQ item 6	1.45	0.59	0.27 to 2.62	0.02
CASQ item 9	1.14	0.60	-0.04 to 2.33	0.06

Model 1, derived from multiple linear regression, contains the optimum set of CASQ items that could be used to predict weight change. For these three items, the regression coefficient (B), along with the standard error (S.E.), 95% confidence interval and corresponding P value are shown.

The second model was fitted, again using the percentage weight change at follow up as the dependent variable. This time there were 21 predictor variables. These included the 12 items of the CASQ, total CASQ score, age, gender, diagnosis, treatment intent plus measurements taken at baseline including BMI, MUST, percentage weight change and C-Reactive Protein. As with the first model, a backward variable selection process was used, fitting all 21 predictor variables into the model. Again, at each step, the variable with the highest P value was dropped and where $P < 0.10$ for log-likelihood ratio tests, the variables were retained in the final model. The second resulting model (Table 5.15) consisted of five variables; CASQ items 4 and 12 relating to enjoyment of food and level of pain, baseline measurements of MUST score, BMI and age. The predictive equation derived from this modelling process is as follows, where the constant regression coefficient is -1.73 and the relative predictive power of the model (r^2) equals 0.26:

% weight change = -1.73 + (CASQ item 4 score x 1.67) + (CASQ item 12 score x 1.69) - (MUST score x 3.40) – (BMI baseline x 0.28) – (Age x 0.09)

Table 5.15: Model 2 determined by multiple linear regression analysis using 21 predictor variables

Predictor variable	Regression coefficient (B)	S.E.	95% confidence intervals	P value
CASQ item 4	1.67	0.49	0.71 to 2.63	<0.01
CASQ item 12	1.69	0.50	0.71 to 2.67	<0.01
MUST score	-3.40	1.19	-5.75 to 1.04	0.01
Baseline BMI	-0.28	0.12	-0.51 to -0.05	0.02
Age (years)	-0.09	0.05	-0.18 to 0.01	0.06

Model 2, derived from multiple linear regression, contains the optimum set of variables that could be used to predict weight change. For these five items, the regression coefficient (B), along with the standard error (S.E.), 95% confidence interval and corresponding P value are shown.

5.2.11.1 Analysis of predicted values and residuals

To determine the robustness of the proposed models, the distribution of the residuals, i.e. the difference in the observed data and computed data calculated from the predictive equation, were explored. Figures 5.9 and 5.10 show that for each model, a plot of the residuals against the predicted values produces a random featureless scatter. These results suggest that the proposed models are indeed linear.

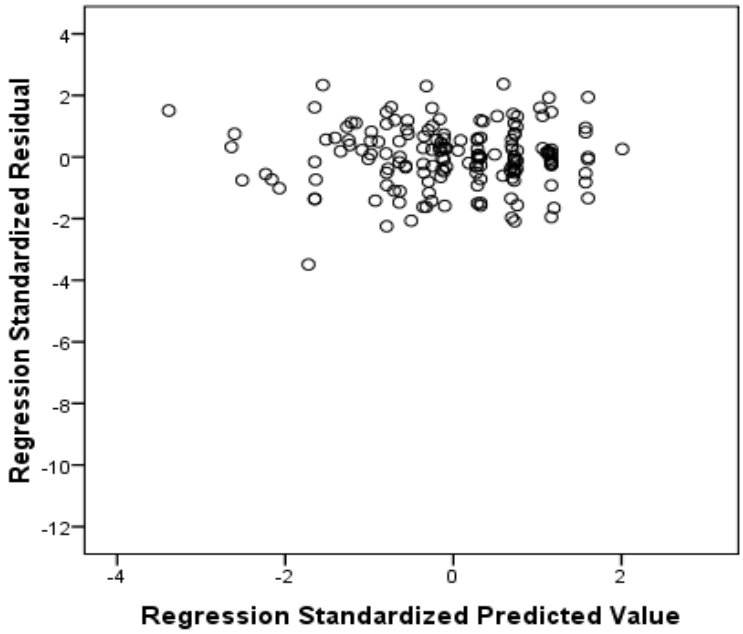

Figure 5.9: Model 1: Distribution of residuals. For model 1, the graph shows the predicted values plotted against the residual values as computed from the multiple linear regression predictive equation.

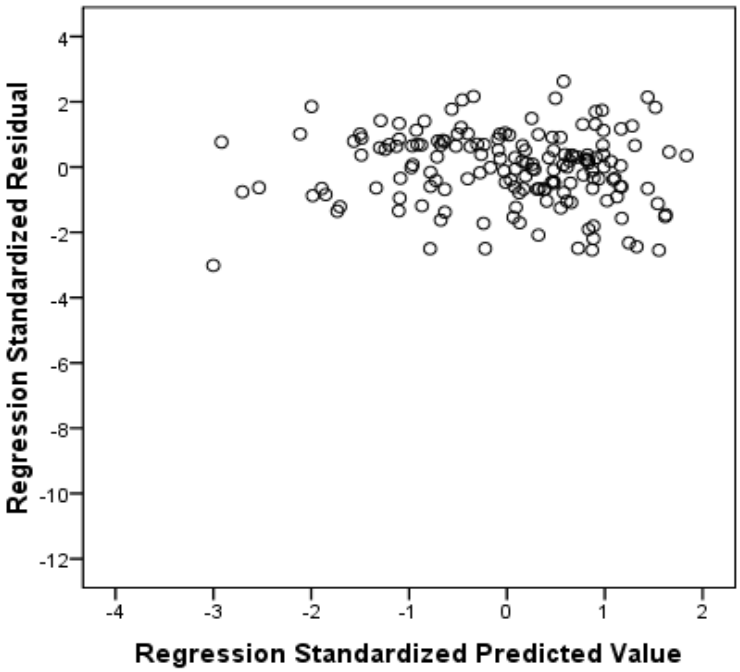

Figure 5.10: Model 2: Distribution of residuals. For model 2, the graph shows the predicted values plotted against the residual values as computed from the multiple linear regression predictive equation.

5.2.12 Cox's regression for survival analysis

To investigate the relationship between the total CASQ score and additional measured variables with survival, a univariate Cox's regression analysis, adjusted for age, was performed (Table 5.16). As to be expected, those who were receiving palliative treatment had a poorer prognosis and were almost four times, and at least twice as likely, to die during the 22 month time period (HR = 3.84, 95% CI 2.02 to 7.28, P <0.001). Participants who had a serum C-Reactive Protein of greater than 10mg/L had a similar, four-fold greater risk of death compared with those who had a low C-Reactive Protein (HR = 3.66, 95% CI 2.16 to 6.18), P <0.001). In addition, results suggested that in the groups of subjects with a MUST score of one, or a MST score of two or more, the death rate was almost twice of that of those deemed at 'no risk' by the screening instruments (HR = 1.81, 95% CI 1.12 to 2.92, P = 0.02 and HR = 1.60, 95% CI 1.01 to 2.53, P = 0.04 respectively). Those participants with a poorer performance status and those who were not eating well, also had a two-fold increased risk of dying. Hazard ratios of less than one, at the 5% significance level, were seen when investigating the outcome of total CASQ score and percentage weight change at baseline. These results imply that for those participants who scored higher on the CASQ, and for those who put on weight during the months preceding the study, there was a smaller risk of dying compared

with those with low CASQ scores, or those who lost weight. Hazard ratios for all other variables, adjusted for age, were not statistically significant at the 5% level.

Table 5.16: Univariate Cox's regression analysis adjusted for age

Predictor Variable	Hazard Ratio	S.E.	95% confidence intervals	P value
Treatment intent	3.84	1.25	2.02 to 7.28	<0.01
C-Reactive Protein	3.66	0.98	2.16 to 6.18	<0.01
Eating poorly	2.01	0.47	1.28 to 3.17	<0.01
Total CASQ score	0.92	0.02	0.89 to 0.95	<0.01
Performance status	1.65	0.30	1.12 to 2.37	0.01
Baseline % weight change	0.94	0.20	0.91 to 0.98	0.01
MUST	1.81	0.44	1.12 to 2.92	0.02
MST	1.60	0.37	1.01 to 2.53	0.04
Social circumstances	1.37	0.39	0.79 to 2.39	0.27
BMI at baseline	0.98	0.03	0.93 to 1.04	0.57
Age	1.00	0.01	0.97 to 1.02	0.79
Gender	0.96	0.22	0.62 to 1.50	0.87
Tumour group	1.02	0.24	0.64 to 1.61	0.95

Derived from univariate Cox's regression analysis, the hazard ratio, standard error (S.E.), 95% confidence interval and corresponding P value for each predictor variable are shown.

To determine the model of best fit, multivariate analysis using a backward variable selection process was used, putting all predictor variables into the model where P<0.1. At each step of the process the variable with the highest P value was dropped. Variables were retained where P <0.05 for log-likelihood ratio tests. The resulting model, adjusted for age (Table 5.17), consisted of four variables; C-Reactive Protein, treatment intent, total CASQ score and percentage weight change at baseline. Each, when adjusted for the remaining three predictor variables, plus age, was an independent significant prognostic factor of survival.

Table 5.17: Cox's multivariate regression analysis for survival adjusted for age

Predictor Variable	Hazard Ratio	S.E.	95% confidence intervals	P value
Treatment intent	4.05	1.64	1.83 to 8.96	<0.01
C-Reactive Protein	2.69	0.76	1.55 to 4.67	<0.01
Total CASQ score	0.93	0.02	0.90 to 0.97	<0.01
Baseline % weight change	0.93	0.03	0.88 to 0.99	0.02

Derived from multivariate Cox's regression analysis adjusted for age, the hazard ratio, standard error (S.E.), 95% confidence interval and corresponding P value for the predictor variables which comprise the final model are shown.

In view of the impact of treatment intent on survival, the Cox's regression analysis was re-run with two groups. The first analysis was performed with participants receiving curative treatment, and the second with participants receiving palliative treatment. Table 5.18 shows the univariate analysis, adjusted for age, for those receiving curative treatment. The results suggested that participants who were eating poorly were five times more likely to die than those whose eating was not compromised (HR = 5.20, 95% CI 1.49 to 18.20, P = 0.01). The only other variable that resulted in a hazard ratio that was statistically significant was related to the social circumstances of participants (HR = 2.30, 95%CI 0.99 to 5.31, P = 0.05). However, as the 95% confidence intervals cross zero it may be assumed that, in terms of survival, there is no real difference between those who live alone and those that do not. Following the multivariate analysis, using the method described above, and when adjusting for age, only 'eating poorly' remained an independent prognostic factor of survival in the curative treatment group (Table 5.19).

Table 5.18: Participants receiving curative treatment: Univariate Cox's regression analysis adjusted for age

Predictor Variable	Hazard Ratio	S.E.	95% confidence intervals	P value
Eating poorly	5.20	3.32	1.49 to 18.20	0.01
Social circumstances	2.30	0.98	0.99 to 5.31	0.05
C-Reactive Protein	6.25	6.05	0.94 to 41.60	0.06
MUST	3.11	1.88	0.95 to 10.20	0.06
MST	1.44	0.56	0.89 to 2.34	0.14
Baseline % weight change	0.92	0.05	0.82 to 1.03	0.15
Baseline BMI	0.92	0.07	0.78 to 1.07	0.27
Performance status	1.89	1.15	0.57 to 6.22	0.30
Total CASQ score	0.95	0.05	0.86 to 1.06	0.38
Gender	0.59	0.40	0.16 to 2.22	0.43
Tumour group	0.69	0.57	0.13 to 3.48	0.65
Age	0.99	0.03	0.93 to 1.06	0.88

For subjects receiving curative treatment (n = 52), univariate Cox's regression analysis was performed. The hazard ratio, standard error (S.E.), 95% confidence interval and corresponding P value for each predictor variable are shown.

Table 5.19: Participants receiving curative treatment: Cox's multivariate regression analysis for survival adjusted for age

Predictor Variable	Hazard Ratio	S.E.	95% confidence intervals	P value
Eating poorly	4.93	3.35	1.30 to 18.65	0.02

Derived from multivariate Cox's regression analysis adjusted for age, the hazard ratio, standard error (S.E.), 95% confidence interval and corresponding P value for the predictor variables which comprise the final model are shown. This analysis included participants receiving curative treatment (n=52).

The results from the univariate analysis, adjusted for age, for those receiving palliative treatment are shown in Table 5.20. For this group of subjects, as with the group as a whole, those with an elevated serum concentration of C-Reactive Protein (>10mg/L) were more likely to die during the study period when compared with those with a normal serum C-Reactive Protein concentration (HR = 2.76, 95% CI = 1.59 to 4.79, P < 0.001). Furthermore, those with lower total CASQ scores and those who had lost weight prior to the study were also at an increased risk of death (HR = 0.91, 95%CI 0.88 to 0.95, P < 0.001 and HR = 0.94, 95% CI = 0.90 to 0.99, P = 0.02 respectively). For this group, following the multivariate analysis, when adjusting for age, total CASQ scores and C-Reactive Protein remained independent prognostic factors of survival in the palliative treatment group (Table 5.21).

Table 5.20: Participants receiving palliative treatment: Univariate Cox's regression analysis adjusted for age

Predictor Variable	Hazard Ratio	S.E.	95% confidence intervals	P value
C-Reactive Protein	2.76	0.78	1.59 to 4.79	<0.001
Total CASQ score	0.91	0.02	0.99 to 0.95	<0.001
Baseline % weight change	0.94	0.02	0.90 to 0.99	0.02
MUST	1.84	0.51	1.07 to 3.16	0.03
Performance status	1.44	0.28	0.99 to 2.11	0.06
Eating poorly	1.56	0.40	0.97 to 2.59	0.07
MST	1.11	0.09	0.95 to 1.30	0.19
Baseline BMI	1.02	0.03	0.95 to 1.08	0.63
Tumour group	0.89	0.22	0.55 to 1.44	0.64
Age	1.00	0.01	0.97 to 1.02	0.87
Social circumstances	1.04	0.24	0.66 to 1.62	0.88
Gender	1.02	0.25	0.64 to 1.64	0.92

For subjects receiving palliative treatment (n = 133), univariate Cox's regression analysis was performed. The hazard ratio, standard error (S.E.), 95% confidence interval and corresponding P value for each predictor variable are shown.

Table 5.21: Participants receiving palliative treatment: Cox's multivariate regression analysis for survival adjusted for age

Predictor Variable	Hazard Ratio	S.E.	95% confidence intervals	P value
Total CASQ score	0.92	0.02	0.88 to 0.95	<0.001
C-Reactive Protein	2.51	0.72	1.42 to 4.42	0.001

Derived from multivariate Cox's regression analysis adjusted for age, the hazard ratio, standard error (S.E.), 95% confidence interval and corresponding P value for the predictor variables which comprise the final model are shown. This analysis included participants receiving palliative treatment (n=133).

5.3 Discussion

5.3.1 Phase II study design

The key objectives for Phase II of the study were to:

1. Obtain an estimate of the reliability of the CASQ.
2. Determine the predictive validity of the CASQ
3. Determine the optimal cut points and overall performance of the CASQ at predicting clinically significant weight loss over three months.
4. Propose an optimum screening instrument to predict clinically significant weight loss over three months.

As with reliability testing, ascertaining the degree of validity that a new instrument has, is essential if it is to be used within a healthcare setting. As there is no single test to determine if indeed an instrument is measuring what it is supposed to, an overall judgment, taking account of several measures of validity, should be made (Streiner and Norman, 2008). In this study, the principal reason for developing a new instrument was to be able to predict which people with cancer, who are not already malnourished, are going to lose weight in the future. Such a tool would allow nutritional treatment to be prioritised and commenced where needed, before the downward spiral of malnutrition, and possibly cachexia, begins. For this reason, one of the key objectives of Phase II of the study was an estimate of the predictive validity of the CASQ, in terms of weight loss over a three month period. As clinically significant weight loss is in practice monitored over a three to six month period (NICE, 2006), and given the fact that this particular population of patients can have a relatively poor prognosis, three months was thought to be an appropriate time interval. An important consideration when conducting a predictive validation study, is that practice is not changed due to the outcome from administering the new instrument. When conducting research within a clinical environment it is often difficult to uphold what is normal practice. To standardise this element of the study,

all participants were offered a booklet on how to improve their dietary intake, irrespective of their response to the questionnaire. Clinic staff were asked to continue with their usual practice with regards to the provision of nutritional advice. This, in some instances, would have resulted in a referral to a dietitian. Despite potentially influencing the weight status of study participants, to withhold this nutritional intervention for research purposes would not have been ethical. Additionally, the presence of a research dietitian in the out-patient clinics may have led to an increased awareness of the nutritional care of patients and influenced outcomes. Furthermore, for those who participated, taking part in a research study about appetite and symptoms could have influenced their actions during the study period. The expected result from these changed actions would have been a decrease in weight loss seen over the study period. As data concerning the nutritional treatment or dietetic intervention for each participant was not collected, the degree to which this may have influenced results cannot be established.

As there is no existing 'gold standard' test for predicting weight loss, it was not possible to determine the concurrent validity of the CASQ. As will be discussed later, to help determine the validity of the CASQ, in addition to establishing its predictive validity, the performance of the CASQ was compared with existing, validated, screening instruments.

5.3.1.1 Phase II study population

Of those potential participants who were initially screened using the MUST, almost one in three (30%) had a score of two or more and were identified as being at high risk of malnutrition. As these people had already lost a clinically significant amount of weight, they were excluded from participating in the study. Using this figure to determine the proportion of patients with lung and upper GI cancer who are at high risk of malnutrition should be approached with caution as those undergoing the screening process were not selected at random or on the basis of, for example, being recently diagnosed. Sampling bias may have had an impact on the results. In addition, directly comparing these results to studies which have used an alternative screening instrument is difficult, as a standard definition of 'at risk of malnutrition' is not available. Moreover, such studies quote the proportion of patients with a single diagnosis, or undergoing a specific cancer therapy, who are malnourished (Segura *et al*., 2005; Isenring *et al*., 2006; Chauhan *et al*., 2007; Renshaw *et al*., 2008). In this present study the figure was calculated across two tumour groups and in patients undergoing both curative and palliative treatment.

It is the intention that the CASQ will be used to predict weight loss in people with cancer. As such it was important for the study sample to be representative of this population (Streiner and Norman, 2008). The study sample was diverse in terms of gender and age and reflected the patterns seen within the cancer population as a whole. Sixty percent of participants were male. This is no doubt due to the type of cancers being investigated. With the exception of pancreatic cancer, lung, oesophageal and stomach cancer are more common in men (Office for National Statistics, 2009). Participants were, almost exclusively, white and British. This broadly reflects the population presenting to cancer services locally and must be borne in mind when interpreting findings (East Midlands Public Health Observatory, 2004). Based on their performance status, most subjects were independent and able to carry out all but the most strenuous activities of daily living. It is possible that those excluded from participating in the study due to previous weight loss may have had a poorer performance status as the two parameters have been shown to be strongly associated in previous studies (Dewys *et al*.,1980; Deans *et al*., 2009). Finally, when considering the reasons why patients (n=16) with a MUST score of one or less were excluded from participating, the main reason was that it was deemed ethically inappropriate by the researcher. Other exclusion criteria, such as ascites or dementia were rare. It should be noted that the validity of the CASQ has not been determined in patients with these conditions.

Participants were chosen on the basis of having a diagnosis of lung or upper GI cancer and, within the study sample, there was a reasonable split between the two groups. It is important to acknowledge that the predictive validity of the CASQ has only been established in this set of patients, and not in all cancer diagnoses. To extrapolate the results to, for example, people with colorectal or breast cancer would not be appropriate (Streiner and Norman, 2008).

The time since diagnosis ranged from less than one month to more than five years. What became apparent during the recruitment phase of the study was that although the majority of patients were currently having palliative treatment, or receiving neo-adjuvant or adjuvant chemotherapy, others had received curative treatment and were possibly, in effect, ‘disease free’. It is important to consider whether these patients should have been excluded from the study. In practice it is extremely difficult to determine if someone is indeed free of disease and there is ambiguity at the point that the decision is made. It is fair to say that, in terms of disease status,

the sample appears to be representative of patients attending a medical oncology clinic.

The objective of the study was to determine the ability of the CASQ to predict clinically significant weight loss and at the planning stage of the study it was considered necessary to have a study population which was relatively stable in these terms, and who were not at high risk of malnutrition. The MUST was used to classify subjects accordingly. One component of the MUST is a calculation of percentage unplanned weight loss over the previous three to six months. This parameter can be difficult to ascertain with any degree of accuracy for two reasons. The first is that the assessor is often reliant on a person's recall of their previous weight, which may or may not be accurate. Secondly, there may be a large discrepancy between percentage weight loss calculated at the three and six month time intervals. For the purpose of the study, the decision was made to record percentage unplanned weight loss over the preceding three months. This may have improved recruitment rates but could lead one to question the stability of the sample in terms of weight loss. Potentially, some participants may have been excluded from the study had weight loss been calculated over six months. If this had happened, whether more or less weight loss over the study period would have been seen is unknown. Ultimately, the outcome of this should not have affected the predictive ability of the CASQ.

5.3.1.2 Baseline nutritional screening

At baseline, the mean weight and BMI of recruited subjects were 74.4kg and 26.0kg/m^2 respectively. These findings differ from previous studies. In a group of 151 patients with gastrointestinal or lung cancer, Khalid *et al*. (2007) found the mean weight and BMI to be lower, 69kg and 24.1kg/m^2. However, the population recruited for the present study excluded those with a BMI of less than 18.5kg/m^2, or those who had already lost more than 10% of their body weight. For this reason it is understandable that the mean weight and BMI were higher in the present study. In fact, over half of subjects had a BMI which classified them as being overweight or obese (WHO, 1998). Despite this, for one in five, their weight loss over the previous three months was between five and ten percent. Although this did not exclude them from taking part in the study, as they were not categorised by MUST as being at high risk of malnutrition, if over a short time frame the weight loss is of clinical significance (NICE, 2006). In practice these findings re-iterate the importance of

determining how much weight someone has lost, and not judging a person's nutritional status based solely on their BMI.

The Malnutrition Screening Tool (MST) was validated in people with cancer undergoing chemotherapy or radiotherapy (Ferguson *et al*., 1999; Isenring *et al*., 2006). This instrument classifies a person at nutritional risk if they have unintentionally lost more than five kilograms, or if they have lost up to five kilograms and have a poor appetite. Almost one third of study participants were classified as at nutritional risk using the MST. In clinical practice, the outcome of this would have been immediate nutritional intervention. This is in contrast to using the MUST where all patients who were identified as needing immediate nutritional intervention had been excluded from taking part in the study. This may lead us to question the guidelines for the use of MUST in this patient population. This issue will be discussed further in section 5.3.5.

Systemic inflammation, as determined by serum C-Reactive Protein, is commonly recognised as a component of the cachexia syndrome (McMillan, 2009). Previous research has established the significance of a raised C-Reactive Protein level (>10mg/L) in terms of reduced function, prognosis and quality of life in people with cancer (Fearon *et al*., 2006). Other studies have found a lower level of greater than 5mg/L as being prognostic of survival (Wang *et al*., 2009). Thirty-seven percent of the participants in the present study had an elevated serum C-Reactive Protein concentration, greater than 10mg/L. This is a smaller proportion than documented in research by Brown *et al*. (2006) which suggests that up to 78% of patients with advanced lung or upper GI cancer may have elevated levels. Variation from previous results may be due to having a truncated sample, where those with noted weight loss, and potentially raised C-Reactive Protein, were excluded. In addition, although the majority of patients studied here had non-curative disease this does not necessarily equate to advanced disease.

In clinical practice, albumin has often been used as a marker of nutritional status. However, as it is a negative acute phase protein, serum levels drop during times of metabolic stress, infection and inflammation. Also, it is affected by hydration status and a long half life makes it inappropriate as an indicator of nutritional status when used in isolation (Chojnowska, 1996). Despite these limitations, serum concentrations of albumin have been shown by some to be a prognostic indicator in terms of quality of life (Vigano *et al*., 2000). In the present study, one in five

participants had a low serum albumin. For the reasons previously discussed, it is difficult to draw conclusions from these findings in terms of nutritional status. However, it may indicate that approximately 20% of this study sample were clinically unstable.

Since this study was planned, and data collection commenced, diagnostic criteria for cachexia have been developed (Evans *et al*., 2008). Applying these criteria to the present study sample suggests that 5% of participants had cachexia. Interestingly, all those who met the diagnostic criteria had a diagnosis of upper GI cancer, and all scored less than 30 (mean = 19) on the CASQ. However, the figure of 5% could be misleadingly low. The diagnosis of presence of cachexia in this study sample was limited to use of the measured variables, i.e. BMI less than 20kg/m^2 or weight loss of at least 5% in 12 months or less, plus three from a raised C-Reactive Protein >5mg/L, albumin less than 3.2g/dL, presence of anorexia or fatigue. Data was not collected to enable an assessment of muscle strength, fat free mass and haemaglobin concentrations.

To summarise, in a sample of 185 people with lung or upper GI cancer who were not at high risk of malnutrition, as categorised by the MUST, the majority were overweight or obese. Despite this, a small number met the diagnostic criteria for the cachexia syndrome and more had a raised C-Reactive Protein level or low serum albumin, all of which carry negative implications in terms of function, quality of life and prognosis. When determining the study sample, the initial aim was to test the CASQ in a population who were not already malnourished, the reasoning being that validated screening instruments, such as the MUST and MST, were already available to identify malnourished patients. Although the study sample aim was achieved when using the MUST to define malnutrition, it was clear from other measured variables, including the MST, that a proportion of the sample may have already been malnourished or indeed cachectic. Overall, this evidence suggests that the sample in the present study was possibly representative of the cancer population as a whole, rather than as intended, only those who were not malnourished. This has implications for the translation of findings. In particular, when defining the population in which the CASQ has predictive validity.

5.3.2 Cancer Appetite and Symptom Questionnaire responses

Completion of the CASQ by 181 study participants provided information on the type, and severity of symptoms experienced by patients with lung and upper GI cancer.

Potential CASQ scores ranged from zero to 48. The mean (SD) score was 30 (7) and the range was from five to 45, suggesting that some patients were indeed experiencing impairment in terms of appetite and symptoms.

Overall, results showed that there was no statistical difference between the severity and the types of symptoms experienced by people with lung and upper GI cancers. This is similar to the findings of Khalid *et al*. (2007) where, aside from appetite loss being more prevalent in those with gastrointestinal disease, they also found no difference in symptoms across the groups at presentation.

To explore the responses to the questionnaire in more detail, the twelve CASQ items can be grouped into three domains; appetite, food intake and symptoms.

5.3.2.1 Appetite

Appetite can be defined as a desire to eat which is expressed in terms of hunger and satiety. Teitelbaum (1964) describes a tri-modal approach to feeding, being regulated by the physical pangs of hunger, the pleasure of eating i.e. appetite, and the satiety which brings about the end of consumption. To add detail to this description, the pleasure of eating can be split into the desire to eat and the enjoyment of food. Responses to CASQ items one to four indicated how participants perceived these subjective experiences.

Previous research suggests that the prevalence of anorexia, or loss of appetite, in patients with lung and upper GI cancer is in the region of 40 to 60% (Khalid *et al*., 2007; McKernan *et al*., 2008; Bovio *et al*., 2009). However, no study appears to distinguish between the different aspects of hunger, appetite and enjoyment of food. In addition, comparisons of figures are difficult due to the heterogeneity of the study samples. Within the present study, item three of the CASQ asked participants to respond to “Before eating I feel hungry…..”. Responses suggested that only around one third of participants regularly experienced the physical pangs of hunger around eating times. Furthermore, results imply that one in five subjects experienced early satiety. Despite this, when asked about their appetite, i.e. their desire to eat, just over half judged this as being good or very good and almost three quarters said that they enjoyed the food that they ate often or most of the time. These findings suggest that within this sample of patients with cancer, there was a marked difference in their experiences associated with these different aspects of food intake.

Experiencing a poor appetite does not necessarily equate to lack of enjoyment of food. These theories will be explored further in Chapter 6.

5.3.2.2 Food intake

A reduction of food intake in patients with advanced cancer, and specifically cancers of the lung and upper GI tract has been reported in the literature (Giacosa *et al*., 1996; Khalid *et al*., 2007; Bovio *et al*., 2009). Differences in the methodology used for collecting dietary intake data can lead to problems with the interpretation of such studies. Furthermore, a clear definition of what constitutes a meal or a snack, and the subjectivity of the terms, may be reasons why the pattern of dietary intake is seldom reported. Hutton *et al*. (2006) investigated the patterns of dietary intake in people with advanced cancer. Analysis from three day diet diaries suggested that 81% of participants ate breakfast, lunch and evening meal. This finding is in contrast with the results of the present study where approximately only two-thirds of participants reported eating three meals a day. Hutton *et al*. (2006) also highlighted the importance of snacking to ensure daily energy requirements are met. Indeed, within the present study, snacking was a frequent occurrence, with 80% having at least one snack a day. A contributing factor to this may be the upper GI diagnoses of subjects, which in practice often results in smaller, more frequent eating episodes due previous gastrointestinal surgery and the presence of adverse gastrointestinal symptoms.

5.3.2.3 Symptoms

People with cancer often experience numerous symptoms, many of which impact on appetite and food intake. Research suggests that symptom burden may change dependent on the stage of disease as well as the treatment pathway (Cooley, 2000; Teunissen *et al*., 2007). In addition, within clinical practice, symptoms often go unrecognised (Yavuzsen *et al*., 2009). Although not a comprehensive list of symptoms, responses to items seven to 12 of the CASQ suggest that the symptom burden in patients with lung and upper GI cancer is high. Previous research appears to focus on specific groups of patients with, for example, lung cancer or incidence of symptoms at presentation (Khalid *et al*., 2007; Lovgren *et al*., 2008; Yavuzsen *et al*., 2009). Although the literature supports the findings in the present study, in terms of the types of symptoms experienced by participants (Teunissen *et al*., 2007), when looking more closely, the proportion of CASQ respondents with reduced energy levels and pain appeared to be lower compared with previous research (Lovgren *et al*., 2008). This could in part be due to the diversity of the sample in terms of stage

of diagnosis and treatment plan. In addition, the sample excludes some patients deemed at high nutritional risk where symptom burden is likely to be greater.

Other symptoms, such as altered taste, nausea and vomiting, are often more commonly associated with anti cancer therapies (Cohen, 2007; Rehwaldt, 2009). Despite this Khalid *et al*. (2007) found that approximately one in five patients who were not receiving treatment experienced taste changes and nausea. Moderate to severe taste changes and frequent nausea were reported by a third of CASQ respondents, highlighting the extent of these problems.

In summary, findings suggest that a high proportion of patients with lung and upper GI cancer experienced symptoms which can impact on appetite. As a consequence, for a considerable number, their eating pattern did not follow the traditional model of three meals a day. Despite this, three quarters of patients regularly enjoyed the food that they ate.

5.3.3 Predictive validity of the Cancer Appetite and Symptom Questionnaire

The predictive validity of the CASQ was examined using Pearson's correlation coefficient. As can be seen from the scatter plot (Figure 5.5), there was a positive correlation between the total CASQ score and percentage weight change. The Pearson correlation coefficient ($r = 0.32$, $P < 0.001$) and regression coefficient ($B = 0.32$ 95%CI = 0.17 to 0.47, $P < 0.001$) support this finding. Within the literature there is little agreement as to what value of r is acceptable. Ferguson (2009) suggests a guideline where r should be a minimum of 0.2 and values of 0.5 and 0.8 represent a moderate and strong association respectively. With this in mind, of the 12 individual CASQ items, half had statistically significant correlations with percentage weight change, where $r > 0.2$. These items were in relation to appetite, early satiety, enjoyment of food, snacks, nausea and pain. However, as with the total CASQ score, results suggest only weak associations between these individual items and percentage weight change. These findings lead one to question the strength of the CASQ as an instrument to predict weight loss in this population. However, as the correlation coefficient is only a marker of a linear relationship between two variables, the ability to draw firm conclusions from these results is limited. As will be discussed in subsequent sections, the association between the total CASQ score, and individual items, was explored further with the use of multiple linear regression techniques.

5.3.4 The Cancer Appetite and Symptom Questionnaire as a screening instrument for predicting weight loss

The ideal screening instrument should be simple, practical and quick to administer. An instrument with these properties is likely to have a higher completion and compliance rate within clinical practice, something which is vital if the screening process is going to have a beneficial impact on patient care. It is hard to dispute the fact that the CASQ fulfils these criteria as it is self-administered by the patient and, by and large, takes no more than five minutes to complete. The optimum screening instrument should also have a high sensitivity, specificity, PPV and NPV. However, in practice, a screening instrument with these characteristics is difficult to develop, and a trade-off between these properties is often required. As it is important that a screening instrument is able to identify those who are at risk, with as few people as possible being missed, a high sensitivity is paramount. In addition, an instrument with a high NPV will mean that for those with a negative test result, it is unlikely that they have been misclassified. The optimum cut point of the CASQ score to predict greater than 5% weight loss was 31/32 (C statistic = 0.64; sensitivity 65%, specificity 62%, PPV 33%, NPV 86%), and to predict greater than 10% weight loss was 29/30 (C statistic = 0.75; sensitivity 71%, specificity 69%, PPV 21%, NPV 95%). In terms of sensitivity and the NPV, it appears from these results that the CASQ is performing at its optimum when predicting greater than 10% weight loss. Specificity at both levels was quite low, suggesting that there would be a number of people wrongly identified as being at risk. When predicting greater than 10% weight loss the PPV was at its lowest, implying that only 21% of patients with positive test results, i.e. a low CASQ score, were correctly identified as being at risk. It is important to consider that the PPV can be dependent on the prevalence of weight loss. A low prevalence could result in a low PPV, despite having an instrument with acceptable sensitivity and specificity (Altman and Bland, 1994). Depending on the agreed intervention for at risk individuals, both the low specificity and low PPV could potentially increase workload and costs, as well as possibly causing unnecessary anxiety for the patient.

5.3.5 Comparison of the Cancer Appetite and Symptom Questionnaire with other screening instruments and variables

Correlations suggested that, in addition to total CASQ scores being associated with percentage weight change, other measured variables were too. Of the variables tested, C-Reactive Protein was found to have the strongest correlation ($r = -0.3$, $P < 0.001$). As serum C-Reactive Protein concentrations increased, so did percentage

weight loss. As highlighted earlier, previous research has established the significance of a raised C-Reactive Protein level (>10mg/L) in terms of reduced function, prognosis and quality of life in people with cancer (Fearon *et al*., 2006; Vigano *et al*., 2000). Other studies have noted that C-Reactive Protein levels are raised in people with lung cancer who have lost greater than 5% weight (Scott *et al*., 1996). Results from the present study concur with those of Mahmoud and Rivera (2002) who found C-Reactive Protein to be positively correlated with weight loss in people with advanced cancer. Certainly, in terms of those patients with lung and upper GI cancer, it appears that this association is not confined to those with advanced disease.

When compared with the CASQ, MUST and MST, C-Reactive Protein as a screening instrument to predict greater than 10% weight loss had the highest sensitivity, specificity, PPV and NPV. Interestingly, the specificity and PPV were at their optimum when a cut point of 15mg/L was used. This is higher than both the upper limit of normality which is used in clinical practice, and the level above which previous studies have used when testing its predictive capabilities.

Results suggested that in the studied population, when compared with the MUST and MST, the CASQ had a greater sensitivity and NPV when predicting greater than 10% weight loss. Both the MUST and MST had a sensitivity of only 50%. This suggests that both instruments would miss half of all patients who were at risk. Although prediction of weight loss was not studied, previous research by Bauer and Capra (2003), when investigating the use of MUST as a screening instrument for malnutrition, found that it was not sensitive enough to be used within the oncology setting. This research was, however, conducted with a relatively small group of in-patients and used subjective global assessment as the 'gold standard'. A more recent comparison of the MUST, MST and the MNA adds further evidence to the fact that the MUST may lack the desired sensitivity within the cancer population (Roulston and McDermott, 2009), although in this study the MST, along with the MNA, was found to be an appropriate alternative. Interestingly in the present study, the highest level of agreement, in terms of identifying those people at risk or not at risk, was between the MUST and MST. Limitations, in terms of an agreed definition of malnutrition need to be considered when interpreting these findings.

To summarise, it appears that, in addition to the CASQ, C-Reactive Protein can be used to predict those out-patients with lung and upper GI cancer who are likely to

experience greater than 10% weight loss over the proceeding three months. For C-Reactive Protein, using a cut point of 15mg/L will give the optimum performance. In addition, when compared with the MUST and MST, the CASQ was better at predicting weight loss in this group of people with cancer. It is however important to consider that the low PPV of the CASQ may mean that in its current format, it is inappropriate for use within the clinical setting.

5.3.6 Determining the optimum model for predicting weight loss

As highlighted above, although the CASQ can predict both 5% and 10% weight loss over three months, its PPV is unacceptably low. This issue may be able to be improved through the refinement of the CASQ, in terms of the number of items included, or the inclusion of additional variables which are predictive of weight loss. If solely focusing on the CASQ, exploratory multiple linear regression suggests that items six (number of snacks), nine (nausea and vomiting) and twelve (pain), combined, result in the optimum screening instrument to predict weight loss. Interestingly, none of these three items consider any aspect of appetite although it can be seen how they all may influence weight change. When considering additional variables, analysis suggests that an instrument containing CASQ items 4 (enjoyment of food) and 12 (pain), along with MUST score, BMI and age are most predictive of weight change. These models would need to be tested prospectively to determine their use within clinical practice.

5.3.7 Survival analysis

Although the primary objective of this phase of the study was to determine the predictive validity of the CASQ, it was of interest to see if the instrument itself, or any of the other measured variables were predictive of survival. Multivariate analysis performed on the whole sample, when adjusted for age, suggested that, in addition to whether someone is receiving curative or palliative treatment, a high serum C-Reactive Protein level, low CASQ score and high percentage weight loss at baseline were all independent predictors of survival. These results concur with those of others studying similar patient populations. On multivariate analysis McKernan *et al*. (2008) found tumour stage, treatment intent, appetite loss and C-Reactive Protein to be predictive of survival in patients with gastro-oesophageal cancer. Also, in patients with inoperable NSCLC, C-Reactive Protein, weight loss, performance status and fatigue have been shown to be predictors of survival (Scott *et al*., 2002). In the present study, when the analysis was repeated in a split sample, the variable ‘eating poorly’ was most predictive of survival for those who had curable

disease. For those with incurable disease, C-Reactive Protein and total CASQ scores remained the most predictive variables in terms of survival. For these analyses it is important to consider the difference in the sample between the two groups. In particular, the number of participants with curative disease that died during the study period was low, 11 compared with 72 in the palliative group. This is likely to have strongly influenced the results of the regression analysis.

5.4 Conclusion

In conclusion, the CASQ has been shown to have predictive validity in terms of future weight loss in out-patients with lung and upper GI cancer. Total CASQ score has also been identified as an independent predictor of survival. As a screening instrument, the optimal CASQ score cut point to predict greater than 5% weight loss is 31/32, and to predict greater than 10% weight loss is 29/30. However, due to its relatively low PPV, routine use of the CASQ within clinical practice must be questioned. A revised instrument, such as one incorporating CASQ items four (enjoyment of food) and 12 (pain), along with age, BMI and MUST score, needs to be tested prospectively. Also to be highlighted is the use of C-Reactive Protein, as both a predictor or weight loss, and of survival. Alternatively, testing the instrument in a more diverse population, rather than one that excluded those who were malnourished as defined by the MUST, may result in improved performance statistics.

CHAPTER 6: PHASE III: A QUALITATIVE EXPLORATORY STUDY

6.1 Introduction

Numerous people with cancer experience a reduction in their food intake which significantly affects their nutritional status, function and quality of life (Fearon *et al*., 2006). In addition, the impact of their weight loss and nutritional problems on their family and caregivers should not be forgotten (Hopkinson *et al*., 2006). Previous research focuses on determining the extent of the problem, as well as trying to provide solutions such as pharmacological and nutritional management strategies. An improved understanding of the experiences and perceptions of people with cancer and their carers, in terms of the factors which influence their nutritional status, may help improve compliance to treatment as well as enabling the development of more patient centred approaches. The key objectives for Phase III of the study were to:

1. Describe the experiences of people with lung or upper gastrointestinal cancer, and their carers, regarding the factors influencing weight change.
2. Explore the causes and influencing factors of weight change in people with lung or upper GI cancer.
3. Propose a conceptual model of influences on weight change in people with cancer.
4. Identify areas for improvement regarding the nutritional management of people with cancer.

A qualitative exploratory study conducted following the principles of the Straussian approach to grounded theory (Strauss and Corbin, 1994) was used to meet these objectives. Theoretical sampling techniques were employed to recruit patients with lung or upper GI cancer, who were participating in Phase II of the study, along with their partner or carer. Data were collected using semi-structured interviews which were transcribed verbatim and subsequently analysed using techniques described in the tradition of grounded theory. Summarisation and interpretation of key categories led to the emergence of core concepts. From this, a theoretical framework relating to the influences on weight change was developed.

6.2 Findings

This section begins with a description of the participants in the sample used for the collection of qualitative data. It goes on to describe the findings from the study. The

following section discusses the categories found to influence food intake. These were ‘symptoms’, ‘self-management’, ‘attitude to body weight’, ‘social support’ and ‘clinical support’.

The core process that emerged from the analysis of the transcribed data was ‘influencing food intake’. The subsequent discussion explains how the interplay between the categories and sub-categories helps to explain this core process. The chapter ends with the proposal of a conceptual model of the process of the influences on weight change in people with cancer.

Direct quotations have been used throughout the discussion to denote the contrary and concurring views of the interviewees. To help maintain anonymity, names used when highlighting quotes are pseudonyms.

6.2.1 Characteristics of the sample

Qualitative data collection took place concurrently with the Phase II study during the 10 months from August 2008 to June 2009. Ten potential interviewees who met the criteria were approached and nine agreed to take part. Listed alphabetically, Table 6.1 describes the characteristics of these patient participants. Initially, sampling was purposeful with Alison and Christine being the first two participants to be interviewed. They were selected based on their diagnosis, social circumstances and weight loss. Following this the intention was to sample patients theoretically. However, not all participants had a spouse or carer available at the time of interview. In addition, the time constraints imposed by the completion of the Phase II study meant that a more diverse study sample, in terms of diagnosis, treatment intent and inclusion of a carer was not achieved. In total five males and four females were interviewed, four of whom were receiving curative, and five palliative, treatment. The sample was diverse in terms of age (range 45 to 77 years) and time since diagnosis (range 3 to 12 months). All but one of the patient interviewees were married, and in each of these cases they were asked if their spouse would like to be involved. Three of the wives of male patients took part in the interviews. Of note is that at the time of interview all but one of the interviewees had a BMI within the healthy parameters (range, 20.8 to 26.3 kg/m^2).

Table 6.1: Characteristics of Phase III patient interviewees

Name	Interview with partner	Age	Marital status	Diagnosis	Months since diagnosis	Treatment intent	1st CASQ score	2nd CASQ score	BMI at interview (kg/m^2)	Study weight change (%)
Alison	No	45	Widow	Oesophagus	3	Curative	25	26	20.9	-9
Bill	No	64	Married	Stomach	4	Curative	32	25	24.5	-11
Christine	No	59	Married	Pancreas	8	Curative	21	25	22.3	-7
David	Yes	63	Married	Lung	9	Palliative	28	28	23.6	-16
Doreen	No	77	Married	Lung	11	Palliative	38	23	23.5	-2
Ian	Yes	59	Married	Lung	7	Palliative	33	29	23.2	-9
Len	No	70	Married	Bile duct	5	Curative	35	24	26.3	0
Paul	Yes	71	Married	Oesophagus	11	Palliative	28	23	23.2	-11
Peggy	No	67	Married	Lung	12	Palliative	35	21	20.8	0

6.2.2 Symptoms

A significant category identified during the axial coding of the transcripts was 'symptoms'. The impact of symptom distress in people with cancer is well documented in the literature (Bovio *et al*., 2009; Cooley, 2000; Grosvenor *et al*., 1989). This is a notion supported by the findings of the present study where all participants talked about symptoms which affected their wellbeing and nutritional intake. Weight loss and a reduced appetite were the most common. However, it was the other symptoms which often contributed to their existence. Table 6.2 shows the 19 symptoms that were expressed by the participants. This category was sub-divided into weight loss, gastrointestinal symptoms, pain, fatigue and psychological symptoms.

Table 6.2: Symptoms experienced by Phase III patients

Symptom	Participant
1. Weight loss	Alison, Bill, Christine, David, Doreen, Ian, Len, Paul, Peggy
2. Reduced appetite	Alison, Bill, Christine, David, Doreen, Ian, Len, Paul, Peggy
3. Vomiting	Alison, Bill, David, Doreen, Ian, Len
4. Pain	Alison, Bill, David, Ian, Len, Paul
5. Nausea	Alison, Bill, Christine, David, Doreen, Peggy
6. Taste changes	Alison, Bill, Christine, David, Paul
7. Reduced energy levels	Alison, Christine, Ian, Paul
8. Anxiety	Alison, Christine, Peggy
9. Early satiety	Bill, Christine, Len
10. Weakness	Bill, David, Ian
11. Tiredness	Alison, Christine, Ian
12. Aversion to smells	Alison, Bill
13. Indigestion	Alison, Paul
14. Constipation	Bill, Paul
15. Diarrhoea	Christine, Len
16. Sore mouth / throat	Bill, Ian
17. Bloated	Bill
18. Hiccups	Paul
19. Feeling cold	Ian

6.2.2.1 Weight loss

All participants made reference to changes in their body weight. Over the course of their treatment some had lost only one or two pounds and, at the time of interview, appeared more concerned about being overweight. For others, the decrease in their weight was an obvious worry for both themselves and their family:

> I was worried about, and the weight was just dropping off.....I thought, I know I've always wanted to be thin but I'm going to be like a beanpole at this rate. (Alison, oesophageal cancer)

> Because I could see him losing the weight then and, you know, he couldn't eat, he couldn't swallow, couldn't sip water, and I says, Is there anything else you can give him? (Ian's wife, lung cancer)

Previous research shows that weight loss can occur at any stage of the cancer journey (Deans *et al*., 2007, Tonouchi *et al*., 2008, Bruce and Hodson, 2004, Andreyev *et al*., 1998) and analysis of these interviews confirmed this. Several of the participants talked about losing weight prior to the diagnosis of cancer being made. For two of them it was one of the symptoms that highlighted that there was a problem. For others, the side effects of treatment; surgery, chemotherapy or radiotherapy, resulted in weight being lost. The analysis of the data from this study suggests that there was individuality to the experience. For example, despite chemotherapy being predominantly associated with adverse symptoms and weight loss, two of the participants put weight on during this period:

> I then had three courses of chemotherapy, which honestly... I went through that absolutely brilliantly. You know, you couldn't, you couldn't fault anything..... And I actually put on weight, over chemotherapy. (Ian, lung cancer)

Most of the participants clearly linked weight loss to the fact that they were not eating the same as previously. In addition, other factors, for example, the ageing process and pre-existing medical conditions, such as diabetes, were also implicated. Overall, the main reasons given for losing weight were associated with the symptoms that patients were experiencing.

6.2.2.2 Gastrointestinal symptoms

6.2.2.2.1 Reduced appetite

Participants experienced an array of gastrointestinal symptoms. The most commonly reported, which was experienced by all of the patients who were interviewed, was a reduced appetite. As previously discussed in this thesis, along with the physiological sensations of hunger and satiety, appetite is one stage in the process of feeding (Teitelbaum, 1964). The subjective phenomenon of appetite, described as the pleasure of eating, encompasses both the desire to eat and the enjoyment of food. In this study the term 'appetite' was frequently used by participants and was often put into context by making a comparison to what they judged as normal:

> Just this pattern: very good appetite, comparatively speaking all the way through to the chemotherapy and then bad appetite after the chemotherapy getting progressively worse. Stopped the chemotherapy good appetite again. (David, lung cancer)

Just over half of those interviewed also directly referred to hunger. One in particular demonstrated the physiological aspect of this sensation:

> [Tummy rumbles] Ah. Did you hear that? That's hungry, that's what I'm doing a lot, it lets me know. (Len, bile duct cancer)

For others, reference was made to feeling, or not feeling, hungry. Two of the participants talked about 'being ready for it':

> And, I wasn't ready for my lunch. I did, I did have a sandwich or something but I wasn't as eager for it. (Doreen, lung cancer)

A desire for food, in those words, was only mentioned by one of the patients:

> I used to enjoy eating chocolate before having the stent, no, and I haven't really got a desire, don't have any desire to eat a lot of chocolate at all. (Paul, oesophageal cancer)

Along the same vein, several participants made reference to what can be construed as a desire to eat, such as "not feeling like eating", or there being "nothing that they

fancied". Additionally, the enjoyment of food was something that was talked about by most. In today's society, where food is available in abundance, enjoyment is a key factor when it comes to eating (Clarke, 1998). In Paul's case, the seriousness of lack of enjoyment of food was evident:

> And the fact that you know you're not going to particularly enjoy it, and you're not sitting down to, if I can use the expression, living to eat, you know, I'm eating just to live. (Paul, oesophageal cancer)

Finally, all three of the participants who had had surgery to remove part, or all, of their stomach complained of early satiety:

> Because my appetite is still as much as it's ever been. But I just get fuller quicker. Obviously, I haven't got the stomach that I had. (Len, bile duct cancer)

Further exploration of the phenomenon of appetite in the data suggested that merely asking someone what their appetite is like will result in a purely subjective, good, bad or non-existent, response. Furthermore, the sensations of hunger, desire to eat, enjoyment of food and satiety may well be mutually exclusive. As such, the focus of any assessment of appetite should include all of these four aspects of the feeding process. Aside from appetite, the taste and smell of food were highlighted as areas of concern for patients.

6.2.2.2.2 Taste and smell

Palatability, or the taste and smell of food, also play an important role in the eating process (Yeomans, 1998). However, the dimensions of palatability in people with cancer are generally less well researched (Bernhardsen *et al*., 2009). Four of the patients who were interviewed in this study spoke about disturbances in their taste which influenced their food intake. All related these changes to times when they were having chemotherapy. Taste changes were described in a variety of ways. Some said that food tasted horrid and others spoke about a lack of taste. A preference for sweet foods was expressed by some. Another participant said foods had a metallic taste:

> And it's very, I know, in my heart, I ought to be having something but because we've got this lack of taste, and what you have got sometimes, like a metallicky taste, but I just don't want to eat. (Christine, pancreatic cancer)

In addition, the off-putting smell of food, specifically meat, was mentioned by two of the participants who were receiving chemotherapy:

> Sometimes the smell of food. I mean, food's never bothered me, the smell of it, even when I've been pregnant. That's never bothered me but this time, it was like, one night I decided I'd do my spaghetti bolognaise and I'd started it and I went to them, I said Helen, I can't do it, the smell, I had to go upstairs out the way, the smell, because certain, meat, probably, you know, was just…(Alison, oesophageal cancer)

> Well, I don't know really, it, the smell, particularly meat puts you off. (Bill, stomach cancer)

Other studies concur with the findings here that patients having chemotherapy may experience altered taste and smell, with these often undisclosed symptoms impacting on both their physical and psychological well being (Bernhardson *et al*, 2008). Overall, research in this area is limited. An improved understanding of the experience and impact of these symptoms could help with the provision of support and self-management.

6.2.2.2.3 Nausea and vomiting

All participants talked about nausea, and/or vomiting. Those with oesophageal cancer also mentioned the discomfort caused by indigestion and hiccups. The analysis suggests that these were symptoms, particularly nausea and vomiting, that had a great impact on nutritional intake and overall well being:

> She'd [G.P.] started me off on some, like gastro- anti-sickness tablets but they weren't working, whatever I took didn't work. And of course, as time went on, I was just being more and more sick, and it got that, sometimes I couldn't keep water down and the weight was just literally, was just dropping off. (Alison, oesophageal cancer)

Although chemotherapy was given by several of the participants as the reason why they were suffering with these symptoms, other causes included the tumour, 'pain relief medication', nutritional supplements and over-eating. Most talked about being given 'anti-sickness medication', and for some this was clearly seen as a panacea:

> But I was feeling sick now and again, and I didn't feel like so much to eat. I did eat, but nothing, not, not as much as I normally did. Especially breakfast. I'd perhaps have my breakfast, porridge and just a couple of spoonfuls and I felt sick. But it was usually middle of the nights I felt sick. But these tablets they gave me were marvellous. It stopped it straight away. (Doreen, lung cancer)

For others, despite changes in the type of medication, these symptoms persisted:

> I felt nauseous today, don't know why....They've had to alter my sickness tablets three times now, because they weren't having any effect. But, we get through [laughs]. (Christine, pancreatic cancer)

One of the patients thought that being sick was an inevitable part of the treatment and this lack of information had prevented her from seeking help:

> .....and the family said I think you should phone the hospital. No, I think it's part of it, if you, you know, and you've got the chemo, it's all this attacking your body. And, like I say, I just persevered with it, and when I went back, and he says, well, really you should have contacted us. (Alison oesophageal cancer)

Others, despite medication routinely being prescribed, did not comply with the anti-emetic treatment. Peggy recounts an observation that she made in the chemotherapy clinic:

> …you've got to approach it with the right, I mean, I did see a lady once when I went that had just had a drip and she was in the waiting room, and she's tearing open the tablets, because she said, Oh, well, I better take one just in case I feel sick, and I thought, you know, just wait and see if you, because the sickness part of it, and I've got three kids, to me, was like the pregnancy

> sickness, the early morning sickness, that was all, just slightly nauseous. Which I still get in the mornings. (Peggy, lung cancer)

Despite wanting to "do as she was told", Peggy later went on to talk more about why she was reluctant to take the tablets:

> The, the slight sickness, I never took any of the big boxes of sickness tablets. The only ones I took, and I didn't take all of those.....I just took two a day, or even one a day, and you know, because I thought, well, I'd better do as I'm told to do. [laughs] And then I noticed they've got some steroids in, so I wasn't too keen on that. (Peggy, lung cancer)

This suggests that compliance with prescribed anti-emetic treatment is variable, a finding that is supported within the literature (Jakobsen and Herrstedt, 2009; Osterberg and Blaschke, 2005). Non-compliance with medication is a phenomenon which has been studied for many years and has implications economically and in terms of health of the individual (Osterberg and Blaschke, 2005). In this case, poor compliance may have been due to the severity of the symptoms experienced, but could also be due to the underlying attitudes and beliefs of the individual. In particular, it appeared that Peggy took a stoical approach to her healthcare and was possibly reassured by the fact that she did not need as much help as other people. Alison believed it was just part of the process and had to be endured. Other people are reluctant to take any medication, sometimes due to the concern over possible side effects (WHO, 2003). As healthcare professionals, assessing the potential concerns of patients which may contribute to the issue of non-compliance could help address this issue. The belief by some patients, that certain symptoms are an inevitable part of the disease or treatment, may be harder to dispel.

6.2.2.2.4 Change in bowel habits

Change in bowel habits, either constipation or diarrhoea, was identified as a concern for several of the participants. Constipation was described as a significant problem by Bill:

> The biggest thing was my bowels, that was, you know, that was terrible, I mean, it was like, fourteen days with not going at all. Oh, it was terrible. You know. Just, you know, you just, and then, I came home and the first … six

> days at home. Well, you felt bloated all the while and horrible. (Bill, stomach cancer)

Patients who had had surgery to resect part of their pancreas referred to issues with diarrhoea. Both had been prescribed Creon to help with malabsorption problems. For one of them this had resolved the symptoms:

> I had to go back and see the surgeon like, three month after the operation, for a check-up and one of his assistants, the young doctor there, he asked me, what the problem was, and I said, Well, I wasn't putting weight on and I was going to the loo. And, he sussed out that that's what it was, and that's what I needed, these Creon tablets. So I'm taking them and I'm all right, everything's all right. (Len, bile duct cancer)

For the other, the symptoms were ongoing and the psychosocial consequences were becoming unmanageable:

> Yeah, well, this is it and it's actually got and I said this the other day its actually got to the point where I don't really want to go out. And that, you get into a vicious circle then. I mean, I went to Lincoln, could be last week, I think with Trevor, and I got in to Lincoln, and I just went into panic mode because I thought, I don't know where the loo is, and it's stupid, I don't know where the loos are. And, then it caused a reaction. [laughs] And I said, I've got to go home, I've got to go home. And I thought, I said we were actually on the point of coming home, I said, No, I'm going to stick this out. But it's, it just causes me stress to go out, I don't like it. (Christine, pancreatic cancer)

In this case, the patient was convinced that the diarrhoea was an inevitable symptom of the chemotherapy which increased her increased anxiety about going out and enjoying normal activities.

6.2.2.3 Pain

Several of the participants talked about experiencing pain. From the analysis it seemed that the causes of pain were variable. One participant talked about a pre-existing condition that caused him back pain. The presence of the tumour, or the treatment given for it, caused physical pain for others. Radiotherapy had made Ian's throat so sore that he was unable to swallow, clearly influencing his food and fluid

intake. He openly expressed the degree of discomfort that he had experienced:

> I've had pain in my life before. You know, because we had a disease called ulcerated colitis. I had that for twelve years until I had all my bowels removed. So I've had pain. But the pain, when you can't even swallow your own saliva, you can't drink and I was having to take this medicine to kill the pain and kill the burning, long enough just to take a drink..... When you got pain like that, the only, the pain I could put it down to, the type of pain, is if you've ever seen the Alien, the film? …It comes out your chest…it started off just there like that and then all of a sudden it was across all your chest and you just felt as though your chest was just going to explode. (Ian, lung cancer)

Another participant, Paul (oesophageal cancer), despite having been on strong analgesics, appeared to play down his symptoms and needed to be prompted by his wife to discuss them:

> Paul's wife: You did have your pain though, Paul.
>
> Paul: I have this pain from having the stent fitted…
>
> Paul's wife: You had a pain that went into his left hand side of his chest.
>
> Paul: …a certain amount of discomfort, some discomfort anyway…but it seems to have settled down a bit. I mean, I was having doses of morphine for a little while, as well as Paracetamols.

This may be linked to the reluctance of patients to disclose the extent of symptom burden, an issue highlighted by other authors (Von Roenn *et al*., 1993) and one which makes the management more challenging.

6.2.2.4 Fatigue

Fatigue is an ongoing issue for many people who have cancer, with some studies reporting up to 60% of patients being affected (Stone *et al*., 2000). Fatigue encompasses several aspects related to quality of life, and as such has physical, cognitive and affective features (Servaes *et al*., 2002). In this study the participants described physical fatigue as feeling tired, having a lack of energy or feeling weak.

The youngest patient to be interviewed discussed her lack of energy the most:

> I mean, that was, it was horrendous, in fact, one morning, I remember feeling that I didn't even have the energy to get up, and I thought, I just want to curl up and die. I have not, I can't put my children through all this, and I just, I didn't even have the energy to get out of bed....(Alison, oesophageal cancer).

Analysis of the interviews suggests that the impact of fatigue was significant, from denying participants the opportunity to continue enjoyed pastimes such as golf, to causing additional physical problems. One person talked about an accident that had occurred as a result of feeling fatigued:

> I mean, I walked all round Clumber Park. I suppose we must have walked about four miles. But, when I was going back, I actually said, I suddenly felt as though I'd hit a brick wall and I just felt very tired and unfortunately, I fell. And I've sprained my ankle badly. But I think that was to do with tiredness, I'd hit this wall and I just, I suppose I wasn't picking my feet up and I fell. And spread-eagled in the mud. [laughs] And I find that even now I get to the point sometimes, I think, I'm hungry that I'm not, I don't really want anything but I know it, all I'm doing is doing a vicious circle because I feel tired. All I want to do is just go to bed. My duvet days, as I call them. [laughter] But I think a lot of that is because of what I'm not eating. (Christine, pancreatic cancer)

In several of the cases, wanting to go to, or stay in bed was the expressed treatment of choice. There was also an association made between a lack of energy and a reduced intake of food. One of the male participants describes a similar experience and belief including feeling unusually cold and spending more time sleeping to overcome symptoms:

> I used to come in [from work], you know, did about six hours at work and came back home or four hours at work and come back home. I used to get into bed, I used to more or less go straight to bed, because I was cold. Because I wasn't taking any food in to burn to give me any energy..... I'd get into bed. I'd get nice and warm, then the next minute, it'd be four hours later. And I couldn't remember dropping off to sleep. (Ian, lung cancer)

Conversely, two of the other male participants felt that the weakness that they were experiencing was due to a lack of activity and mobility. One of them, a farmer, felt that getting back to his normal routine was going to help get his strength back:

> Yeah, getting back on to my legs has been the biggest problem. You know, I have to be careful I didn't fall over. I mean, being in all the time, you know, it's…that's been the trouble, getting some air into your lungs. You know. Now, with working again, like I'm, out again, like you know, I'm getting better, you know. (Bill, stomach cancer)

The physical dimensions of fatigue were clearly expressed by the study sample. For most, the resulting effect was a reduction in activity. Winningham and colleagues (1994 cited by Armes *et al*., 2004) propose a model of fatigue in which a decrease in physical activity is an important determinant when considering the impact of symptoms on the development of fatigue. It is likely that the subsequent effect would be a decrease in functional status.

In the present study, only one participant mentioned a lack of motivation, and this was in relation to carrying out routine tasks such as cooking. Cognitive aspects, such as loss of concentration or attention were not included in the discussion. That is not to say that these aspects of fatigue were not significant, just that they were not raised in relation to the nutritional issues discussed.

6.2.2.5 Psychological symptoms

In addition to the physical symptoms experienced by people with cancer, psychological and emotional symptoms are often present (Butt *et al*., 2008). In particular, symptoms of anxiety are common and have been shown to have a negative impact on quality of life (Stark *et al*., 2002; Brown *et al*., 2009). Generally, such symptoms may be less well expressed and, if unaddressed, may impact on the emotional well being of the patient and their carer (Kennifer *et al*., 2008). In this study, in relation to nutritional factors, there was a gender difference in the reporting of psychological symptoms, with the men being less likely to disclose these feelings. Several of the female participants did express feelings of anxiety, worry and stress. For one, the anxiety was caused by not being able to eat and losing weight:

> ..... it was only through me being so, like I say, lethargic, I was worried, because I knew I wasn't getting the nutrients, I wasn't getting anything into my body..... I was worried about, and the weight was just dropping off...(Alison, oesophageal cancer)

For others it was the other way round with the anxiety being perceived as the root of the reduced appetite and intake:

> The appetite had gone as well. It was, I just didn't want, I just didn't want to eat. Or, if I get something in front of me and I think, Oh, I couldn't eat this, or I might eat half of it and the rest of it go in the bin. But I think, some of that was due to anxiety.....One of the biggest losses [in weight] was over that period when they told me that the cancer had returned. Now whether that was anxiety, that's when I started to have this big drop and since then, it's been dropping. (Christine, pancreatic cancer)

The perpetual nature of anxiety causing weight loss, and weight loss causing anxiety was pointed out by another participant:

> And, it's sort of a little bit of a vicious circle but, say, I weighed myself and then, I'd lost a pound, or a pound and a half, I mean, I did, although my scales aren't accurate, as I said, a pound and a half, two pound, then you start to panic or you start to worry, and then, because you're worrying, you don't feel hungry. (Peggy, lung cancer)

In addition to expressing feelings of anxiety, emotional upset, and the impact on her husband, was also talked about by one of the women:

> I mean, I find the emotional side of it terrible some days. And, for no apparent reason, there doesn't seem to be any reason, I just get very, very upset. So, it's all par for the course....it's part of the treatment, you know, and I accept that but some days it's quite difficult to, and of course, it doesn't help then, because then, my husband gets upset it's a vicious circle, but [laughs]. (Christine, pancreatic cancer)

Although not directly linked to the discussion of nutrition, the spouses that were interviewed also talked about the worry or upset that they felt at times:

> ....and then, the following morning, Ian says to me, I can't fight this no longer, and I think that was our lowest, weren't it?…think we both got upset then. (Ian's wife, lung cancer)

In one case, the extent of the impact on the family caregiver had led to emotional support being sought:

> It's very hard to come to terms with. Well, when we did come to terms with it in the fact that we were putting all our expectations on having the operation in March and then when that door was slammed, I think that's when we really sort of felt, well, what else is there? I must admit I was traumatised for quite a while, and the GP was very good to me and so was the Macmillan nurse. And I go now to a support group. (Paul's wife, oesophageal cancer)

Finally, other emotions expressed by participants included shock, fear and frustration. At the time of diagnosis, three of the patients talked about feeling shocked. Len also disclosed that he felt scared. Reasons given for feeling frustrated varied. Alison was frustrated because, despite feeling hungry, the nausea and vomiting was preventing her from being able to eat. For Bill it was not being able to get out on his farm:

> [I am feeling] probably a bit niggling, can't get out the house all the time, you know. See things you want to do and can't.....Yeah. That's the biggest trouble. You want to do something that you can't do. [laughs] (Bill, stomach cancer)

In summary, findings from this study sample confirm the high number of physical and psychological symptoms that are experienced by people with cancer, supporting what has previously been reported in the literature (Cleeland *et al*., 2000; Teunissen *et al*., 2007). The analysis of this study data highlights how these symptoms can impact on appetite, food intake and weight status. In addition, there is the acknowledgement of a vicious cycle of symptoms where one may perpetuate the next, as in the case of anxiety and anorexia. Although there are clusters of symptoms which are common to a specific cancer or treatment, there is certainly uniqueness to the experiences of an individual. Furthermore, some people view certain symptoms as an inevitable part of having cancer and are therefore less likely to seek advice from a healthcare professional. Others may play down the extent or

their ailments or may have pre-existing conditions which impact on their symptom burden.

To minimise the negative impact of physical and psychological symptoms on food intake and overall quality of life in people with cancer, it is the responsibility of the healthcare professional to ensure that a comprehensive assessment of all symptoms is conducted as part of routine clinical care. Considering the number of screening and assessment tools that are available, it is unlikely that there will be universal agreement on the detail of the assessment process. It is important to remember, as demonstrated in this study, that there is great individuality to the symptom experience.

6.2.3 Self-management

Another category that emerged from the analysis of the interview transcripts was the self-management strategies used by participants to maintain or improve their weight. A framework for self-management theory has developed over several decades and is grounded in the assumption that individuals self-care to maintain health and wellbeing (Orem, 2001). Discussion and study of this theory has increased over recent years, with self-management being used in the clinical setting to help improve the treatment of chronic conditions such as cancer (Larson *et al*., 1999), obesity (Butryn *et al*., 2007) and asthma (Myers, 2002). In the U.K., self-management features highly within the NHS Plan in helping to promote a patient-centred health care service (Department of Health, 2004; Department of Health, 2005). In this study, two sub-categories were identified relating to self-management. The first was self-monitoring using weight or other observations. The second was the changes that were made to dietary habits, by individuals and by their carers, in order to help manage their condition.

6.2.3.1 Self-monitoring

Within the literature, the term self-management has become interchangeable with self-care, self-action and self-monitoring. Within this context, it should be emphasised that self-monitoring is indeed one aspect of the self-management framework (Wilde and Garvin, 2007). Strategies for self-monitoring include observation, measurement and recording of certain parameters, such as weight, along with a personal awareness of changes in symptoms, activities of daily living and cognition (Wilde and Garvin, 2007).

Self-monitoring of weight was something that all participants in this study did. However, this was not always done using weight as the measured parameter. Change in the fit or size of their clothing was one of the first markers of weight loss for some people. Observation of the shape or size of their body was another. Within the study sample two of the participants weighed themselves daily:

> Well, no, I jump off and on every day [laughs]. I don't actually write it down… (Peggy, Lung cancer)

Others talked about weekly or less frequent measurements. Of the three who did not check their weight at home, two had previously never done so, and Alison (oesophageal cancer) had deliberately decided not to have scales in the house due to having a teenage daughter. Although there was sometimes an absence of the use of weighing scales, it was clear that other self-monitoring techniques, such as observation of appearance or fit of clothing, were being used:

> Was probably size fourteen, yeah, probably fourteen, I'd gone down a little bit over Christmas, so I probably a size fourteen then.....I notice like my clothes were getting too big and then, all of a sudden, I'd say it was quite, from January to say probably the mid, beginning of March, it wasn't too bad a weight loss but then after that, it was quite rapid. It seemed to sort of, I really dropped down like another dress, size eight, size ten. (Alison, oesophageal cancer)

For men, rather than relating this to the size of their clothing, the observations were made in terms of the use of belts or braces:

> But, look at the belt now.... those two are the ones I normally use [pointing to the buckle holes in his belt]. When you all of a sudden, you have to start and make extra holes, there and there…(Ian, lung cancer)

Some of the participants also made reference to how they had noticed changes in the appearance of parts of their body:

> Yeah. I mean, I'm surprised actually, I can just get my hand round my wrist it, and that's something I haven't been able to do since I was about twenty eight [laughs]. (David, lung cancer)

> ....and I knew with like my face, because I've got quite a rounded face and my face was just like quite sunken as well.....But I know when my face goes drawn, that I've not been eating, because it just tends to go from there, you know. (Alison, oesophageal cancer)

Both of the participants who weighed themselves daily alluded to the fact that constant self-weighing may be having a negative impact:

> As far as my weight is concerned, it was at ten [stone] two [pounds] in November. Every time I had chemotherapy, I seemed to put three or four pounds on, went straight up three or four pounds straightaway, but some of it tailed off, but I managed to push my weight up, on our scales anyway, to about ten ten, weighed in the morning ..... we've monitored almost too closely, don't we? (Paul, oesophageal cancer)

A number of different reasons were given by participants as to why self-weighing took place. For some of them it was habit and had started prior to their diagnosis of cancer:

> Well, we used to weigh regular anyway. My wife started that off. She's always trying to keep her weight down. (Len, bile duct cancer)

Others began following the commencement of treatment and kept a written record of their progress:

> I usually stick to once a week rather than popping on the scales every day, I mean, I didn't used to, that was part of the problem.....but I have kept a record, actually, over, ever since I came back, soon as we came home from hospital, just to see, out of interest really, how it's doing. (Christine, pancreatic cancer)

Analysis suggested that where weight loss was not perceived as an issue, self-monitoring was conducted to help prevent weight gain:

> Well, it's levelled off round nine stone, because I think, I did put some on at Christmas and I ain't got that off. [laughs] ....but I always weighed me with my clothes off. Now, they weigh, at the hospital, they weigh me with

> everything on, like. So that puts a few pound on, don't it? (Doreen, lung cancer)

Wilde and Garvin (2007) conclude that the aim of self-monitoring is to create an awareness and understanding that will facilitate a change in action, or guide clinical intervention from a healthcare provider. Certainly, a change in behaviour, as a consequence of the self-monitoring process, was discussed by one participant:

> But, yes, I do monitor it. But, when I have lost, say, a pound, again, I think, well, if you eat, it will help…(Peggy, lung cancer)

Also, following the observation of weight loss, Alison sought advice from a healthcare professional:

> I was worried, because I knew I wasn't getting the nutrients, I wasn't getting anything into my body. And that was when I said, can't you, I saw a nurse ..... I actually mentioned that, because I was worried about, and the weight was just dropping off (Alison, oesophageal cancer)

Not all participants were involved to the same degree in self-monitoring of weight status. In this sample, gender differences were apparent throughout the participant's discussion of self-monitoring of weight. All but one of the women interviewed weighed themselves at home. The one who didn't believed that having weighing scales in the house was a threat to her young daughter. Furthermore, it appeared that the men that self-monitored their weight were encouraged to do so by their spouse:

> I weigh myself daily. And I have to report [laughter]. (Paul, oesophageal cancer)

Within the literature there is a dearth of information regarding the use of self-monitoring in nutrition support for undernutrition and cachexia. No reference was located that refers to the recommended techniques or frequency of self-weighing in a nutritionally compromised cancer population. Despite the lack of guidance, some individuals take it upon themselves to engage in this activity. Anecdotally, dietitians in the U.K. recommend self-monitoring of weight, where deemed appropriate, usually on a weekly basis. However, there is ongoing debate as to the aptness of

this, particularly with patients receiving palliative treatment. Studies exploring the use of self-monitoring in obesity management have highlighted the possible negative psychological implications, in terms of altered mood and self esteem, of regular self-weighing (Ogden, 1996). Certainly within this study, it appeared that those who weighed themselves daily had an almost obsessive attitude to any small changes in their weight status. Within the cancer population, particularly when the concern is around deterioration in nutritional status, research is needed to identify the potential advantages and disadvantages of this aspect of self-care. Further exploration of the concept will provide valuable knowledge which will enable the healthcare team to educate patients as to the most appropriate techniques.

6.2.3.2 Change in dietary habits

In this study it was clear that several of the individuals had adapted their dietary habits in an attempt to alleviate symptoms or to improve their weight status. These findings concur with those of Hopkinson (2007) who describes a theory of self-management related to changes in eating habits made by people with advanced cancer. In this study most individuals changed from what they perceived as a healthy diet to one that included unhealthy foods. One of the participants here expressed this with a note of satisfaction:

> I'm eating, I'm eating now more fattening things than I've been doing, previously. Because all of a sudden, I've got license to eat those things because I'm not putting weight on. .....But now, I tend to be a bit relaxed about it and have some biscuits or a cake, because, the satisfaction of knowing I'm not going, I'm not putting weight on. (Len, bile duct cancer)

For others, having to miss out fruit and vegetables and choose unhealthy foods in order to deal with unpleasant symptoms resulted in feelings of concern:

> So I was literally living on 'Shortie's' biscuits at the time. [laughter] Not very good for the, but that's all I could manage to keep down was a plain biscuit with lots of sugar on, to try and keep the energy level..... I mean, I've always loved fruit and vegetables, but I found I couldn't eat a lot of fresh fruit, I was trying to eat like, I mean, it'd take me about an hour to eat a banana. (Alison, oesophageal cancer)

The importance of continuing to include healthy foods in the diet was also expressed by those caring for individuals:

> ....but he has to have some [vegetables]. Because it's important for his nourishment. So I try and put a bit on for him and he can get just a little bit down it's better than none, isn't it? (Paul's wife, oesophageal cancer)

Similar observations, where an individual's beliefs about the types of foods that should be eaten could not be achieved, have been made by other researchers (Hopkinson, 2007). Negative feelings, such as guilt and anxiety, associated with these changes in eating behaviour may be detrimental to both the patient and their carer resulting in conflict within the relationship. Furthermore, as the focus is on prioritising low energy density, high fibre foods, weight status may be adversely affected.

Aside from changing the composition of the diet, other self-management strategies, such as changing the meal pattern or texture of the food, were used to influence dietary intake. These activities were often initiated, and talked about, by the female spouses:

> I think it's going to come though, to having smaller meals, more frequently. Rather than having a pattern of breakfast, lunch and dinner, he's going to have to have something, perhaps, more substantial at eleven o'clock, something more substantial at four o'clock. (Paul's wife, oesophageal cancer)

Finally, although not a change in dietary habits per se, one of the participants also disclosed how, following the observation of the action of a friend, she changed the way she managed her medication:

> Well, I was taking it, all I was told was to take one before I had a meal, or with a meal. So I was actually taking it with my meal. I have a friend, actually, who's had the same operation, she's also on Creon, and I know she always takes hers sort of part way through her meal, so I thought, Oh I'll do this. (Christine, pancreatic cancer)

In summary, the findings of this study suggest that individuals with cancer, and their family care givers, employ personally devised self-management strategies in an attempt to improve their nutritional intake and status. An individual's underlying knowledge and beliefs about diet and healthy eating may play an important role in their decisions regarding the self-management of nutritional issues. Furthermore, previous research suggests that variables such as demographics may also impact on the ability of an individual to self-manage their condition (Dodd and Dibble, 1993). Whilst some individuals make these changes willingly, for others, decisions to move away from what is perceived as a healthy diet may be shrouded in anxiety. Factors influencing self-management strategies used by people with cancer to address nutritional problems need to be explored further. In practice healthcare professionals should be aware that patients may be employing these techniques and should include a discussion of, and support, their use.

6.2.4 Attitude to body weight

Attitude to body weight was another category identified during the axial coding of the transcripts. Body image *per se* is an area which is often researched within the cancer population with previous research regularly focusing on the negative psychological impact of weight loss and its meaning (Poole & Froggatt, 2002). In the present study, attitudes to body weight were mixed, with an apparent gender difference. Generally, participants talked about their body weight, often relating it back to their 'normal' or pre-illness status. For women, despite having lost weight due to illness or treatment, being thin was still seen as desirable. Weight maintenance was their aim, gaining weight was not. Following their diagnosis of cancer, all of the women that were interviewed appeared to have an optimistic attitude towards weight loss:

> I went to this particular dinner, I put the outfit on that I hadn't worn for a few months and I suddenly thought, Oh, oh, that fits a bit better. You know, because I knew in my heart that I should be doing something about it, because it just, it had gradually crept on over the last couple of years..... But, so, as I said, it's more of the fact of losing the weight really now, I mean, I don't, I don't want to put on what I had on, but I also want to, I'd like to see it levelling out a little bit, you know. (Christine, pancreatic cancer)

> .....it was great, to tell you the truth, it was great all the, I can't admit any other, the weight loss was just, oh, I'd love to stay like that..... (Alison, oesophageal cancer)

Although Peggy commented that she wished that she had this figure when she was twenty five, she clearly associated weight loss with negative consequences. This observation has been commented on by other researchers (Hopkinson, 2006):

> .....well, whether it means it's the beginning of the end, once you start losing an awful lot of weight, I don't know. (Peggy, lung cancer)

The attitude of trying to maintain what they classed as a desirable weight was echoed by two of the male interviewees. However, they only talked about how they had struggled to maintain their weight prior to being diagnosed with cancer:

> The year before, yeah. And, and, I was very pleased, eleven [stone] four [pounds], I could still get into all my, you know, things were good, it was good. But of course, when we were on [the cruise], I come back and I was a bit more and a bit more and sort of getting up to eleven [stone] ten [pounds] and all, and eleven [stone] twelve [pounds] and that's what I was. I was struggling to keep under, I was working and doing whatever singing and doing whatever I could to keep my weight down. But actually, I was about eleven ten or eleven twelve. (Len, bile duct cancer)

Once diagnosed with cancer, the male interviewees who had lost weight tended to focus their discussion on trying to put weight back on and were generally hopeful that this would happen:

> As I say my weight's gradually come back up. It dropped after the first session I went down to ten four, so I managed to get a couple of pounds on in the first three weeks. On, in the first week, sorry. That's the first week of it, and then, again, it's ten four. And ten five so I just, gradually, just gradually coming up in the first few sessions of chemo (Paul, oesophageal cancer)

Throughout these discussions only one talked about the importance of weight gain in terms of getting his strength back:

> I'm hoping to put it back on again.....mind you, I've lost it on my legs, that's where I've lost it. In my legs and arms..…ain't lost any fat, it's just muscle I've lost. (Bill, stomach cancer)

These findings suggest that attitude to body weight is one factor which may contribute to an individual's overall perception of body image. This in turn may impact on their desire to eat, and food intake. It may be postulated that, previous to their diagnosis of cancer, the women, and some of the men, had issues around body image, or more specifically, body size. As previous research suggests, in any population this is not unusual, with women being more likely to be dissatisfied with their body image than men (Algars *et al*, 2009).

Finally, although exploration of body image *per se* was not a key objective of this study, other dimensions of this construct were highlighted by some of the participants. Peggy had worked in the theatre for many years. She talked in detail about changes in her physical appearance:

> Well, I keep thinking my face looks very haggard..... my teeth are completely sort of destroyed, and that, the chemo does affect them a bit too, doesn't it? And I think because I've got no teeth they're so, I look in the mirror sometimes, I think, God, you know, I look really gaunt. But I haven't lost any weight, so I think, again, it's all in the mind..... I don't think my hair, well, I can't really tell now because it is so overgrown, I don't think it's ever quite got back. It breaks off very, very easily. (Peggy, lung cancer)

Whereas Bill, who lived and worked on a farm, associated changes with a loss of function:

> I've lost it on my legs, that's where I've lost it. In my legs and arms..... Weaker, yeah, yeah.....as I say, I've not been using them, that's half it all.....Sort of sitting round for a month ain't me. (Bill, stomach cancer)

The analysis suggests that gender differences may be significant when considering attitudes to body weight and image, a hypothesis from body image theory which is supported by the literature (Algars *et al*. 2009). It is likely that these variations may stem from aspects of evolutionary theory where female attractiveness and male

strength were valuable reproductive attributes. Today, it is probable that images presented in the media reinforce these primitive traits, relating to the perception of body image in both men and women (Groesz *et al*, 2002; Hargreaves and Tiggemann, 2009). As established by Price (1992), it is important to consider that individuals with cancer may have pre-existing issues around body image. Long standing attitudes to body weight may impact on their perception of risk, related to weight change. What is seen by a healthcare professional as being a significant decrease in weight may be viewed by the individual as a positive part of the cancer experience. In these situations, dietary counselling with an aim to increasing weight needs to be handled sensitively, with open discussion as to the potential benefits of weight maintenance or gain. What must be considered, when working with people with cancer, is that their values and previous social construct are liable to play a role in their feeling of self-worth and attitude to body image.

6.2.5 Social support

Social support was another category that was identified during the analysis process. In relation to nutritional intake, most study participants talked about friends or family who provided support regarding food and nutrition. More specifically, one area which emerged through the analysis of the data was the provision of meals by family members. Some of the male and female patients discussed how they prepared the households meals. For others it was their spouses who usually took on this task. The wife of one of the male patients expressed some of the challenges around taking on this responsibility:

> And it's a shame, because I try to give him lots of variety, more things that I know that that he could, or he should obviously be able to eat, but there's no pattern. Sometimes he'll eat his fish, lemon sole, easily, other times he finds difficulty with it. So there isn't actually a set meal that you say well, he's definitely going to be able to eat this, it varies from day to day. Sometimes you're able to have a bit of beef, aren't you? Or chicken. But there's no guarantee in the time that I cook for him that he's going to actually be able to eat that.... And that's disappointing, very disappointing for him. But also, very demoralising for me. I have spent a lot of time trying to cook something you think, well, that'll be all right, and that's got good nourishment and it should be fairly easy to eat but it doesn't turn out that way. (Paul's wife, oesophageal cancer)

Previous work suggests that the gender of the patient, and their family caregiver, may influence the level of satisfaction when it comes to providing support around the preparation of meals (Locher *et al*., 2009). In this study, as only female spouses were interviewed, confirmation of this theory is not possible. However, there were similarities in the findings in relation to the frustration felt by one of the female caregivers at her husband's inability to eat her meals. Indeed the findings of this study suggest that family care giving is not without its problems. Concern at the deterioration of her husband's condition, when she was supposed to be looking after him, was expressed by another of the female caregivers:

> And also, and then, you know, how difficult it is for the carer to try all sorts of different things, to try and encourage…encourage them to eat. And at what point do you say, Come on, let's chivvy you and let's get you going, because you're just going downhill rapidly, and you don't want that to happen, in a sense, on your watch. [laughs] As it were. And you're not, I'm not nurse-trained, I used to be an occupational therapist, so you know, there's that going on in the back of my mind knowing that you know I've got to keep his mood up and also his strength, and this is just not going to help. (David's wife)

One of the male participants used humour when referring to a situation where his wife had been disappointed by his inability to eat her cooking:

> Now, my wife, funny what happened, my wife said you don't want to eat that when I get you home you don't have to eat that horrible hospital food. And when I came home, I went off my food. And she couldn't believe it because she'd seen me eat, how I'd eaten in hospital..... And then, when I came home and I wasn't eating her cooking, well, I wasn't very popular [laughter]. (Len, bile duct cancer)

Another of the participants was a widow and lived with her teenage daughter. In this situation, where there was the absence of a spouse, there were indications that other female family members were involved in aspects of care giving around eating and meal times:

> I know people are trying to help and, like my mum says, I'll do you some liver and, you know, like I say, I can only manage a little bit but I'll try anything if I

> think it's going to, especially if it's to get me some energy.....And my daughter was doing the smoothies as well, like, with strawberries and banana and I found I could drink them so I knew I was getting my fruit down me and I enjoyed them and she was putting like ice in it and everything, they were lovely. (Alison, oesophageal cancer)

The analysis suggests that family members also unwittingly provide support. An example of this was discussed by one of the women:

> Last night I had quite a good meal. My son and his partner came over and I ate , what I would call a normal meal last night, you know, but, today's not so good today. I can't actually……think, Oh, I could sit down and I could really enjoy that meal. I mean, I ate my meal last night and I did eat it all and I suppose, because we had company as well, it makes a difference, you're not…but it's, because I suppose we had company last night, it takes your mind off it a little bit....Yeah, you were talking, I was eating, which was, which is logical, I suppose [laughs]. (Christine, pancreatic cancer)

Some of the other participants also talked about going out to eat at restaurants:

> You know, I've been out with the children for a couple of meals which I couldn't, just before I started the chemo, I mean, the last time was the end of May, my eldest son was home from the marines and he took me and my daughter to the pictures and we went in Nando's first and I says, oh, I'll just have three chicken wings and I'd manage one and I had to run to the toilet and all night, I wasn't very well. And Tim said, I'm going to take you home, I went, no, it's not defeating me like this…but about three or four weeks ago, we went in Nando's and I had the three chicken wings and I managed nearly three of them. (Alison, oesophageal cancer)

> You know, we've been out recently and quite often, I'll have pâté or something, just to, a starter, just, just for my meal rather than the main course, things like that. (Paul, oesophageal cancer)

Despite having to adapt eating behaviour, continuation of this social activity appears to be important.

In addition to talking about support provided by family members, participants also received advice from friends and family. For some, the advice was difficult to follow:

> My mother in law's tried to get me to eat Corrigan moss because she's Irish. [laughter] And I went, no way.....I think it's like a seaweed that they boil up and when it's done, it becomes white and it looks like white porridge and it sets like a jelly. [laughter] I says to her, I will not eat that.....But no, people have tried to say Oh, eat this, like friends, eat this, eat that, but it's not, if you don't fancy it as well, you've got, I think sometimes you do have to fancy it. (Alison, oesophageal cancer)

For others the advice helped:

> I got introduced to them [Fortisip], a friend of mine's other half has got pancreat- anyway, got it somewhere like that and he felt sick the whole time and couldn't eat. So, he got put on those, and his wife called in to see me at the shop one day and she said, oh, Jack's got these, you know, if you don't, if you can't, you know, you feel a bit nauseous, she said, he lives on them. So anyway, I had one and I thought, well, I don't drink milk because I, me and milk don't really go together, but I had the banana one and I really enjoyed it. And, anyway, so I, you know, have those. (Peggy, lung cancer)

In summary, the findings from this study suggest that the family members are involved in the day to day provision of nutritional care of patients. Negative aspects of the role of family caregivers were not expressed by the patients, although the analysis suggests that some of the female caregivers, at times, found providing this support a challenge. In addition to providing practical support, patients receive advice around what to eat from family and friends, advice that they may choose to try to follow, or not. Observation at the time of interview suggests that without such support and encouragement, some patients' nutritional intake would deteriorate further. That said, the burden on the carer must not be forgotten. Contrary to the findings of other studies, here none of the patients expressed negativity at the support that had been offered around eating and drinking (Hopkinson and Corner, 2006). Eating is often seen as a social event, and for some, this is lost when appetite and food intake deteriorate (Hopkinson and Corner, 2006). Despite experiencing adverse symptoms around eating, going out to restaurants was still an important activity in patients' lives. As theorised by others, this activity may be linked

to wanting to maintain some sort of normality and the associated belief that this is a sign to themselves or others that they are fighting the cancer (Shragge *et al*., 2007). On a practical level, the unwitting support offered by family and friends, which engage the patient in eating as a social activity, may be a valuable strategy in the improvement of food intake.

6.2.6 Clinical support

Clinical support was the final category identified through the analysis of the data. All of the people interviewed in this study sample, since being diagnosed with cancer, had regular reviews with a healthcare team. The professionals that were talked about by the participants included oncologists, G.P's, nurses and dietitians. During the axial coding, two sub-categories linked to clinical support emerged from the data; monitoring and nutritional advice.

6.2.6.1 Monitoring by the clinical team

Guidelines within the U.K. recommend that all patients are weighed on admission to hospital, at their first attendance at an out-patient clinic or when there is any cause for concern (NICE, 2006). Therefore, it is not surprising that most of the patients interviewed made reference to having their weight monitored by a healthcare professional at some point in time. Monitoring of weight occurred in the in-patient and out-patient setting, although the frequency of this cannot be established. For some patients, being weighed was an indication that body weight was something that needed to be checked:

> Well, I've never took any notice until they started weighing me at the chemo clinics, like. (Bill, stomach cancer)

For others, it gave reassurance that their weight was not a concern at that point in time, but potentially caused anxiety by the suggestion that weight loss was inevitable:

> And when I went in to have my operation, she said, a week you know, they weigh you and everything, she said, Oh, you're right on, you're within the parameters and she says, you've got a nice weight to go into it, because she says you are going to lose some weight, but she says I think I was just on the top line of…. (Christine, pancreatic cancer)

Regrettably, even when decreasing, regular monitoring of weight did not always equate to acknowledgement of a problem or to the provision of nutritional advice:

> Nobody had seen me, I mean, they was weighing me but nobody had actually [seen me], it was only through me being so, like I say, lethargic. (Alison, oesophageal cancer)

This is a finding supported by other researchers who found that in the out-patient setting, referral into dietetic services was inadequate (Baldwin *et al.*, 2006).

Undoubtedly, regular monitoring of body weight by healthcare professionals does have advantages in terms of helping to identify, and monitor, those patients who are in need of nutritional support and intervention (NICE, 2006). It may also be a reassurance to the patient and their carers that their weight loss is being monitored. Additionally, where a change is detected, self-management strategies may be implemented to address these issues. However, as was seen in this study, despite a significant decrease in weight being identified by the healthcare professional, further action is not always taken. It is essential, not only for patient satisfaction, but also for improving outcomes, that there are protocols and services in place which lead to the provision of individualised nutritional assessment, counselling and intervention in these cases.

Although not highlighted as a major concern by this group of patients, consideration must also be given to the potential distress caused by the activity of weighing (Hopkinson, 2007). For some individuals, their family and carers, weight loss is seen as a sign of disease progression, with constant monitoring leading to increased anxiety (Poole and Froggatt, 2002; Reid *et al*., 2009). Particularly for those with advanced disease, discussion as to the benefits of regular monitoring of weight should take place.

6.2.6.2 Nutritional advice from the clinical team

Several of the participants talked about receiving nutritional advice from nurses, doctors, dietitians or nutritionists. Specifically, since being diagnosed with cancer, three of the patients interviewed had received advice from a dietitian. Whilst in hospital, Paul had seen a dietitian following the insertion of his stent. He appeared happy with the timing of the referral and the information that he had received. He had also been told by his G.P. that a referral could be made to a dietitian should he

so wish. Despite this, he was still losing weight and the nutritional supplements that he had been prescribed by his G.P. were probably lower in energy density than those that would have been prescribed by a dietitian:

> I chatted to the G.P. this afternoon, went to get some, another prescription for the Ensure drink. And, he were just talking to me generally how I was and saying well, if I want to chat more with the dietitian, he'll arrange it for me. The thing at the moment if I can keep on eating solids then I prefer to. (Paul, oesophageal cancer)

One interpretation of his final comment may be that he believed that if he saw a dietitian she would advise him against eating solid food, possibly resulting in a reluctance to access this service.

As discussed above, despite losing weight, Alison had to ask the oncologist if she could speak to someone regarding her diet. Following this she saw a dietitian on a couple of occasions where ways of increasing the energy density of her diet, as well as modifying the texture, were discussed. She was also prescribed nutritional supplements. Although Alison appeared pleased with the advice she had received, she was unable to comply with some aspects. In particular, the advice to puree her food was not followed:

> I used to do it for the babies when I, you know, do the food, it was all fresh food and everything and I used to purée it all down and taste the thing, mm, you know, that's, I think it's, I don't know whether it's the thought I've worked with it, and then the thought of, I've got to eat that, and I'm thinking, well, it's only like, you know, it's all the foods together, but I tried it a couple and I couldn't eat it. And I thought, my poor babies. [laughter]..... I think it was the thought and then with the taste of it, I think, all the tastes together, you know, like if you, I tried to do the broccoli and a bit of potato and I did liver, Mum had done me like, liver and again, to try and get that, and she'd done liver in gravy and I thought oh, I'll purée it up, oh, oh no, I just can't. Yet I could eat it just as it was. (Alison, oesophageal cancer)

Intake of texture modified diets in patients with dysphagia, due to the appearance, taste and texture, is traditionally poor (Wright *et al*., 2005). Alison's experience, and Paul's reluctance to move away from solid foods, suggests that this is also the case

in people with cancer. The psychological aspect of likening the texture to the food that you eat as a dependent baby may be of issue.

Compliance with prescribed nutritional supplements, in terms of type and quantity, was also a problem for some of the participants. Ian had been provided with a bag of supplements by the radiotherapy department but was disappointed that there had been nobody available to talk to at that point about his diet. He finally saw a dietitian when his swallowing had deteriorated to the point that he was unable to swallow his own saliva and compliance with the advice was impossible:

> Fortisips and Fortijuce. I tried to take them. I managed to get them down about two or three times but every one of them made me sick. (Ian, lung cancer)

Like Ian, Christine had been prescribed nutritional supplements without the assessment and support of a dietitian. She described being given 'a bag from the hospital' and the difficulty she had taking them. Despite having lost 'three stone', Christine was still waiting to see a dietitian:

> When I came to clinic, they [oncologist] actually said, well, you're still losing weight. But I had, I hadn't lost as much as obviously I have now but, she, she said, well, try the Fortisips and they gave me some in a bag from the hospital..... I try and have, as I said, one or other, I mean, I think they mentioned to me the other day they thought I ought to be having three a day. And there's just, I don't think there's any way I could cope with three, because she said, well, that'll give you nine, about nine hundred calories. And, I can manage one a day over a, spread out, but I can't, I don't think I could cope with three. (Christine, pancreatic cancer)

Assessment, individualised treatment and monitoring by a dietitian have been shown to minimise inappropriate prescribing practices, and have financial benefits (Skinner and Smith, 2008). Regardless of this, the analysis from the present study suggests that there is inappropriate use of nutritional supplements in clinical practice and, despite having seen a dietitian, none of the three participants were receiving ongoing monitoring or follow-up.

In addition to receiving nutritional advice from a dietitian, some of the participants described the advice that they had got from other members of the healthcare team. Following surgery, one of the men that was interviewed remembered being given a leaflet and had been told to eat 'little and often'. The advice given by another healthcare professional to another of the patients was less reliable:

> I put myself onto pineapple because they said about the time when I went to oncology that's when the manager said pineapple will help you with your appetite, pineapples, and I went and got [laughter] loads of pineapple so I was trying to eat that ..... (Alison, oesophageal cancer)

Finally, in addition to a lack of dietary advice, one participant talked in detail about the problems that she had experienced related to one of her prescriptions, and the mixed messages that she had received from the two teams involved in her care:

> But, of course, I'm taking the Creon because they've removed part of the pancreas, and unfortunately, they never gave me the leaflet, I had been taking it five months and they didn't give me the leaflet to tell me how I should be taking it.....And the other thing that's happened is in this last week is they've actually taken me off another medication that the hospital where I had my surgery said I've got to take for life which is, I think is Lanzoprazole. Because the Oncologist tells me that they've, the two don't mix. .....So what they've done, they've actually, on Tuesday, they've told me not to take it anymore. But I'm in a bit of a cleft stick in actual fact, because the nurse from the first hospital tells me I ought to be taking it. (Christine, pancreatic cancer)

In summary, analysis of the data suggests that the experiences, in terms of the nutritional monitoring and advice that the participants of this study received, were variable. Prescribed nutritional supplements had been given out without a detailed assessment, resulting in non-compliance and waste. In addition, for those who did see a dietitian, there were issues around the timing of nutritional advice. Despite these factors, unlike the findings from other studies (Hopkinson and Corner, 2006), patients were generally pleased with the advice that they had received. However, compliance with dietary treatment was not always achieved. Due to the absence of ongoing support and monitoring from the dietetic service, non-compliance, or further nutritional problems, failed to be recognised. In order to improve the nutritional

treatment and advice given to patients, changes in the provision of services needs to occur. Routine screening for nutritional deficiencies must be implemented to ensure that all patients who are at risk of malnutrition are identified in a timely manner (NICE, 2006). In addition, services need to be in place to allow for the individualised nutritional assessment, treatment and ongoing monitoring, by a dietitian. Finally, to improve the patient's experience, consistent and reliable treatment advice is essential.

6.2.7 Understanding the influences on food intake

As a result of the analysis of the transcribed data, the core process that emerged was 'influences on food intake'. The categories and sub-categories previously discussed in this chapter connect and interrelate. This allows an explanation of what influences the food intake in people with cancer to be made. Analysis of the relationships between the categories led to the conclusion that the influences on food intake were a fluid process. They could change from one time point to the next depending on, for example, the treatment being received or the physical and psychological state and circumstances of the individual. Although there was a clear individuality to the lived experience, it was evident that these experiences came from a shared reality. The following discussion summarises this core process.

The final analysis showed that weight loss could occur at any stage of the cancer trajectory. For some patients, a significant amount of weight was lost prior to being diagnosed with the disease and was one of the first signs that there was a problem. Having surgery was another time when weight loss was likely to occur. The increase in symptom burden surrounding chemotherapy or radiotherapy also led to some patients losing weight, although this was not a universal experience.

Monitoring of weight was something that happened during hospital visits, seemingly on a regular basis for those receiving chemotherapy treatments. However, the nutritional treatment of patients who had lost weight was managed, at best, in an ad hoc, untimely manner with few patients being referred to dietetic services, and none receiving the necessary ongoing support and monitoring. Dietary advice and nutritional supplements were prescribed by several members of the healthcare team. Patient compliance was variable, with the palatability of sip feeds as well as the inability to take a pureed diet being commented on as barriers.

In addition to having their weight measured at the hospital, self-monitoring of weight status was common. Males and females were involved in this act although it appeared that for the men this was something that was encouraged by their spouses. In addition, the frequency of self-weighing varied. It was evident that, for some, becoming obsessed by their weight was a concern. It was less clear whether it helped or hindered motivation to eat and ultimately maintenance of weight status, and this needs to be explored further.

Gender difference was also apparent when considering attitude to body weight. Although the women acknowledged that they did not want to lose any more weight, they appeared pleased to have lost weight as a consequence of their illness. On the other hand, the men felt confident that they would be able to put back on what they had lost and were more likely to link the weight loss to a decrease in their function and strength.

Food intake was clearly influenced by the presence of adverse symptoms. At some stage of the disease process and its treatment patients experienced a reduction in appetite. More specifically, their desire to eat and enjoyment of food was affected. In addition, the physiological pangs of hunger were reduced and, for those who had had gastrointestinal surgery to remove part of their stomach, there was an increase in early satiety. Nausea and vomiting were other commonly experienced symptoms which greatly impacted on food intake. Either occurred at any time point and was not solely associated with chemotherapy. This is contrary to the experiences of changes in taste and aversion to smells which were specifically linked to times of chemotherapy treatment. Along with other commonly reported complaints such as bowel problems, pain and fatigue, the impact of symptoms on both the patient and their carers lives was significant, affecting them both psychologically and socially. Symptoms such as anorexia, nausea and vomiting undoubtedly affected the experience of going out to eat. However, it was clear that this was still an important part of life and despite having to make adjustments to their food choices, something that patients persevered with.

Men and women mostly appeared happy to discuss their experiences of physical symptoms although some of the men seemed more reluctant to talk about the bowel problems that they had been having or the extent of their pain, particularly when in front of their spouses. In addition, the psychological and emotional distress experienced as a consequence of the disease was only addressed by the female

patients and female carers, suggesting a gender difference in the reporting of this issue.

In addition to receiving advice from healthcare professionals, patients certainly attempted to self-manage their symptoms and condition. In terms of manipulating food intake to overcome issues of weight loss, nausea or vomiting, this included making changes to the types of food eaten as well as the portion sizes and texture. However, these changes were often misinformed as the emphasis appeared to be on eating a 'healthy' diet, high in fruit and vegetables and low in fat and sugar, principles which, for someone at nutritional risk, are inappropriate. A sense of guilt surrounded the inability of the patient to follow healthy eating guidelines, this was alongside frustration from caregivers who felt that it was important to aid their recovery.

Family and friends evidently offered their advice and support to help encourage food intake. The conscious offers of help may or may not have been able to be implemented by the patient. It is likely that the unconscious efforts, such as sitting down to a meal with the patient thus distracting them from the eating process, or encouraging them to partake in social activities, may have helped the most. Finally, for those caring for someone with cancer, the challenges that arose, including those associated with food intake and nutritional status should not be underestimated.

6.2.8 A conceptual model of the process of influences on weight change in people with cancer

A conceptual model of influences on weight change in people with cancer is proposed to help illustrate the relationships between the categories (Figure 6.1). The model was developed from the five categories that were identified in the data, namely 'symptoms', 'self-management', 'attitude to weight', 'social support' and 'clinical support'. In addition to the relationships between these categories, the model presents the theory that food intake, and hence weight, is influenced by many things. Overall, these factors which may act to motivate, or de-motivate the eating process resulting in an increase or decrease in food intake, are specific to the individual and in a state of constant flux. What follows is a discussion of the relationships between the elements within the model, as well as explanation as to how the qualitative data supports this framework.

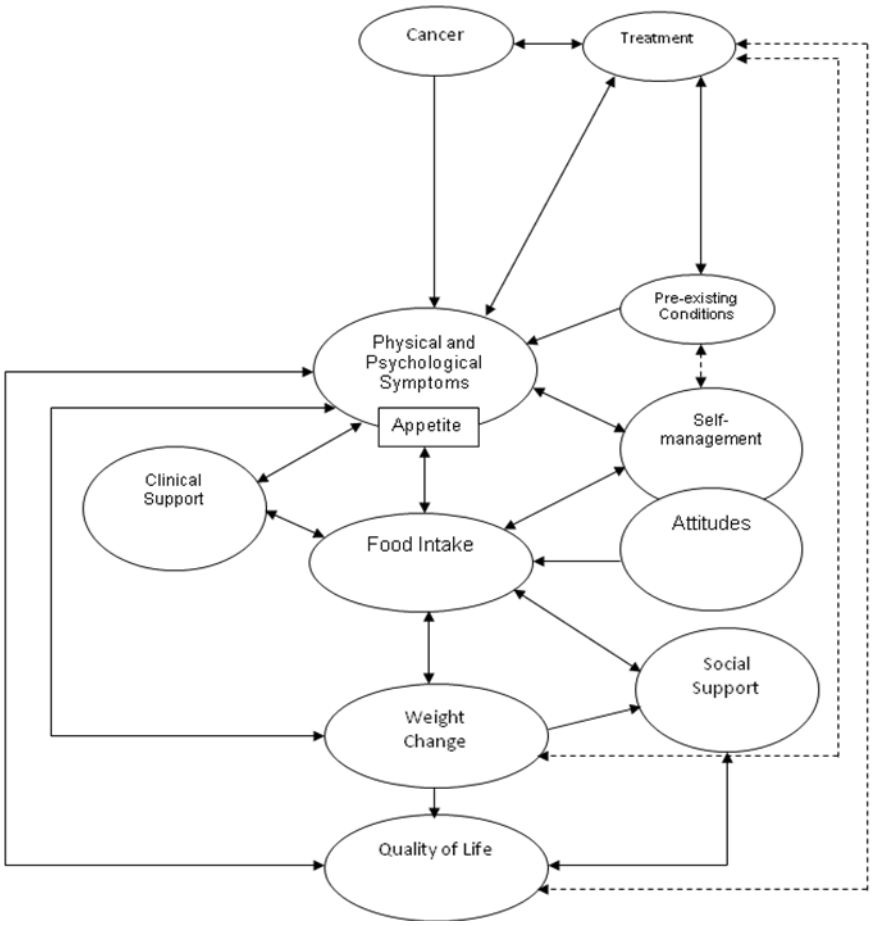

Figure 6.1: Conceptual model of the process of influences on weight change in people with cancer. Solid line, relationships noted in the data; dotted line, existing hypotheses.

The disease itself will be one of the factors which determines what treatment will be given to the patient. Both the cancer and its multimodal therapies can result in numerous adverse symptoms. In addition, many people with cancer will also have pre-existing co-morbidities which may be contributing to the symptom burden. The aim of any treatment will be to cure or palliate the cancer, and along with this will hopefully come a reduction in symptoms. The findings of the present study showed that many of the participants experienced an array of physical and psychological symptoms caused by a combination of the tumour and its treatment. Furthermore, for one patient, the significance of ongoing pain from an old injury was evident in the data. It was clear that at different times of the disease and treatment trajectory, the severity and consequences of such symptoms varied, and for some, following

treatment, there was a definite improvement in symptom burden. For others the opposite was true, with chemotherapy, radiotherapy and surgery being implicated as causal factors.

As found in the study data, and the existing literature, many patients with cancer experience a reduction in appetite (Teunissen *et al*. 2007). For some this may be a symptom in isolation, but for others the decrease in appetite is as a consequence of other symptoms such as nausea, vomiting or anxiety. Yet another group of patients may continue to have a good appetite, despite experiencing such problems. This phenomenon was explained by some of the participants in the study whose food intake had been decreased as a consequence of early satiety and vomiting but who continued to express feelings of hunger and desire to eat.

Whatever the cause of the symptoms, it is likely that there will be an impact on the nutritional intake of the person. In turn, even small adjustments to food intake may positively or negatively impact on the burden of symptoms such as nausea or vomiting. If ongoing, the conscious or subconscious adjustments to food intake will result in a change in weight in either direction, ultimately impacting on function and quality of life. Findings from this study, and others, demonstrate how malnutrition and weight loss can impair quality of life in people with cancer, varying from an inability to pursue favourite pastimes, to a loss of independence (Nourissat *et al*., 2008). Impairment in nutritional status and quality of life may then directly impact on the level of symptom burden. This was seen in the present study where weight loss and reduced functional capacity probably resulted in increased symptoms of anxiety and fatigue.

Self-management strategies employed by individuals may directly improve food intake. For example, in the present study, participants changed their eating pattern or attempted to include more energy dense foods. Indirectly, self-management techniques may also lessen the symptom burden. An individual's attitude is also likely to influence nutritional intake in either direction. Indeed, findings from the present study represent how attitude to weight and body image can impact on a person's food intake. The data also supports the theory that self-management and attitude were inter-related concepts. The findings suggest that the approach taken to self-management was affected by the individual's attitudes and beliefs, this was particularly seen by those taking a stoical approach to managing their condition.

In this context, social support relates to the support that an individual receives from family or friends. This may be in terms of the practical assistance offered such as preparation of meals, encouragement, or the giving of knowledge with the intention of enabling more appropriate food choices. This support, depending on the level and reliability, could result in either an increase or a decrease in food intake. It was evident from the current study that for some, without the assistance of their spouses, food intake would have deteriorated further. For those offering support it is likely that observation and awareness of the individuals' changing food intake and weight informed their help and advice.

Clinical support can also directly or indirectly influence nutritional intake. Here clinical support refers to the support and advice that are provided from a member of the healthcare team regarding the nutritional management of the patient. Quantitative research tentatively shows that this type of support, such as the provision of dietary information or the prescription of nutritional supplements, can increase nutritional intake (Stratton *et al*, 2003; Baldwin and Weekes, 2008). This was also suggested by the findings of the present study where participants reported an improved intake following advice. In addition, providing advice and treatment for adverse symptoms may also lead to an improvement in appetite and ability to eat.

In summary, when nutritional intake is negatively affected, the results can be catastrophic. This may present as weight loss and malnutrition and is followed by a reduction in function and ability to conduct the normal activities of daily living. In addition, the psychosocial implications need to be considered. The discussed conceptual model aims to demonstrate the perpetuating and complex nature of the influences on weight in patients with cancer. A greater understanding of the factors which influence nutritional status may help in the provision of support.

CHAPTER 7: FINAL DISCUSSION AND CONCLUSIONS

7.1 Introduction

The methodological approach and results of the individual three phases of the study have been discussed in the preceding sections of this thesis. The purpose of this final chapter is to assimilate and summarise the overall key findings. In addition, limitations to the project will be discussed and what has been learnt regarding the research process will be highlighted. The chapter will conclude with a discussion of the implications for clinical practice and areas where further research is warranted.

7.2 Study rationale

Malnutrition is common in patients with cancer, particularly of the lung and upper gastrointestinal tract (Chauhan *et al.*, 2007; Bozzetti, 2008; Halliday *et al*., 2009). In addition, the number of people who have the cachexia syndrome is likely to be significant (Laviano et al., 2005; Fox *et al*., 2009). Those who experience such symptoms are in a state of negative energy and protein balance caused by a combination of reduced nutritional intake and abnormal metabolism. The resulting effect is weight loss, muscle wasting, fatigue and psychological disturbances all of which may increase morbidity, impair quality of life and reduce survival (DeWys *et al*., 1980; Capuano *et al*., 2008; Nourissat *et al*., 2008; Swinton *et al*., 2008). Currently, there are no satisfactory treatments for cachexia. However, an increased knowledge of the underlying pathophysiology is allowing new therapies to emerge. It is probable that improved patient outcomes are more likely if these treatments are offered alongside conventional nutritional support and before significant weight loss has occurred. A better understanding of the complex processes that have an effect on weight change in people with cancer, along with a simple means of identifying patients at greatest risk of future weight loss would help to target such an approach. Existing screening instruments can help to identify those who are already malnourished (Bauer *et al*., 2002; Stratton *et al*., 2004; Isenring *et al*., 2006). However, within the literature, no tool when tested with people who have cancer appears to be predictive of weight loss.

This study used a mixed method exploratory approach to develop a deeper understanding of the complex factors that have an effect on, and can predict, weight change in people with cancer. Phases I and II were conducted sequentially and used quantitative methodology to test the reliability and validity of the CASQ. Phase III, an exploratory qualitative study following the principles of grounded theory, was

conducted concurrently alongside phase two. The key objectives which were achieved were to:

1. Obtain an estimate of the reliability of the CASQ.
2. Determine the predictive validity of the CASQ
3. Determine the optimal cut points and overall performance of the CASQ at predicting clinically significant weight loss over three months.
4. Propose an optimum screening instrument to predict clinically significant weight loss over three months.
5. Describe the experiences of people with lung or upper gastrointestinal cancer, and their carers, regarding the factors influencing weight change
6. Explore the causes and influencing factors of weight change in people with lung or upper GI cancer.
7. Propose a conceptual model of influences on weight change in people with cancer.
8. Identify areas for improvement regarding the nutritional management of people with cancer.

7.3 Summary of findings

The aim of the following section is to integrate the findings from all three phases of the study and to discuss and summarise the key points. Noteworthy is that the objective of the qualitative phase was to understand the range of views held by the participants regarding their dietary intake and weight. It is therefore not appropriate to make claims about the distribution of those views across a population. This means that the findings are not generalisable in the quantitative sense. However, findings from the qualitative data analysis clearly indicate the experiences and challenges of the participants, and their carers, in terms of managing their weight status, thus adding to our understanding of this phenomenon.

7.3.1 The experiences of people with lung or upper gastrointestinal cancer, and their carers, regarding the factors influencing weight

7.3.1.1 A vulnerable population

An improved understanding of the experiences of people with lung and upper GI cancer, and their carers, regarding the factors influencing weight change came from the findings of the Phase II and Phase III studies. The results indicated that this population was extremely vulnerable in terms of risk from nutritional related concerns and malnutrition. Although limited by the lack of a consensus definition of

malnutrition, this is a finding that is undisputed by previous research (Laviano *et al*., 2005; Bozzetti *et al*., 2009). In the present study, despite recruiting people not deemed at high risk of malnutrition as defined by the MUST, at recruitment, almost 50% of the Phase II sample was identified as at risk by the validated MST. In addition, during the study's three month follow-up period, 55% of participants lost weight. The low total CASQ scores obtained from a number of the patients (total CASQ score ≤31, n = 94) further supports the conclusion that those patients with lung or upper GI cancer experience multiple appetite and symptom related problems, a finding that is supported by the existing literature (Teunissen *et al*., 2009). It is also noteworthy that the Phase II study data suggest that, in terms of symptoms experienced, there were no significant differences between the responses of those patients who had lung cancer compared with those who had upper GI, a finding that concurs with the findings of others (Khalid *et al*., 2007).

The impact of the symptom burden was also explicit throughout the Phase III study data. In particular, our comprehension of this phenomenon has been enhanced by being able to appreciate the individual complexities of the lived experience as well as the self-management strategies employed by patients trying to deal with their situation and disease. The findings from the present study regarding symptom burden and self-management techniques concur with those found by other researchers (Hopkinson, 2006; Hopkinson, 2007). For example, previous work has proposed a theory of self-management of changing eating habits in people with advanced cancer (Hopkinson, 2007). As concluded from the present study, it is likely that the promotion of self-management techniques by healthcare staff may help patients to facilitate self-action, and ultimately gain an improved sense of well being.

7.3.1.2 Malnutrition, an unrecognised problem

The lack of awareness of malnutrition and its consequences have been realised for decades. Florence Nightingale wrote about such concerns in the 19th Century: 'Every careful observer of the sick will agree in this that thousands of patients are annually starved in the midst of plenty, from want of attention to the ways which alone make it possible for them to take food …… have a rule of thought about your patient's diet; consider, remember how much he has had, and how much he ought to have to-day' (Nightingale, 1860). In truth her observations could well have been written in the present day. It was evident from the analysis of the qualitative data in

the present study that, despite the identification and risk of malnutrition being raised as important issue in several national and international policy guidelines (NICE, 2006, ESPEN, 2006, BDA, 2009), patients' nutritional needs were still going unaddressed in clinical practice. Despite losing weight, several of the participants interviewed had not received advice to help address their nutritional concerns. These are findings that are supported by larger quantitative research studies (Kelly *et al*., 2000; Baldwin *et al*., 2006). A recent document published by The British Dietetic Association highlights the key role of the dietitian in ensuring that malnutrition is both recognised and treated (BDA, 2009). However, as discussed in the document, addressing the issues of malnutrition within the hospital and community settings needs a coordinated multidisciplinary approach. Findings from the present study suggest that there may be some way to go before this important area of healthcare is effectively managed.

7.3.2 Development and validation of the Cancer Appetite and Symptom Questionnaire

Research suggests that in the cancer population the majority of patients, particularly those with gastrointestinal disease, experience symptoms which impact on their ability to eat and ultimately their weight and nutritional status (Laviano *et al*., 2005). Hence, in this group of patients where the prevalence of malnutrition is so high, the need for nutritional screening in clinical practice should be questioned (Elia, 2005). It is important to consider that in addition to identifying patients who are malnourished, other reasons for implementing a screening instrument may include raising awareness of the issue and prioritisation of workload. Within this field, recently published research continues to focus on the validity testing of existing malnutrition screening instruments within specific cancer populations (Gioulbasanis *et al*., 2008; Roulston and McDermott, 2008; Stoyanoff *et al*., 2009). To date there remains no conclusion as to which is the most appropriate instrument to screen for malnutrition in the clinical setting. It is likely that an instrument with predictive capabilities would aid intervention in a more timely manner. Although other researchers have investigated how weight loss *per se* may be able to predict morbidity and mortality (Temel, 2004; Fearon *et al*., 2006), little has been published postulating what variables, if any, are able to predict those who will lose weight. A recent small study (n=58) in a group of patients who had cancer aimed to identify what factors were able to predict involuntary weight loss. However, due to the study being published only in abstract form it is not possible to determine the actual methodology used, or the detail of what combination of variables were found to

predict weight loss (Blum *et al*. 2009). Within the literature, no screening instrument could be located which is able to predict patients with cancer who are at risk of future weight loss, making the current study investigating the predictive validity of the CASQ, unique.

Earlier research, using content validity testing with an expert panel, led to the development of the 12-item CASQ from the previously validated Council on Nutrition Appetite Questionnaire (CNAQ). When tested for reliability with the Phase I study participants, the internal consistency and test-retest reliability was acceptable. To determine the predictive validity of the instrument, field testing within the Phase II study population suggested that the optimum cut point of the CASQ score to predict greater than 5% weight loss was 31/32 and to predict greater than 10% weight loss was 29/30. Noteworthy is the similarity of the cut points for predicting these two different degrees of outcome. The CASQ was performing at its optimum when predicting greater than 10% weight loss. Here the sensitivity of the instrument was 71%, specificity 69%, positive predictive value (PPV) 21% and negative predictive value (NPV) 95%. In combination, the findings from Phases I and II of the present study suggest that the CASQ is reliable and can predict weight loss over three months. However, the low specificity and low PPV imply that some patients would be incorrectly classified as being at risk, potentially increasing workload and costs, as well as impacting on anxiety levels of the patient and their carers. In addition, compared with the validity testing of other malnutrition screening instruments, the performance of the CASQ was found to be sub-optimal (Isenring *et al*., 2006; Stoyanoff *et al*., 2009). Overall, the study results imply that in its current form the 12-item CASQ is not appropriate for use within clinical practice.

Finally, it is also important to consider if it is actually possible to predict weight loss in this cancer population. It is feasible that there are unknown underlying processes which resulted in the CASQ lacking predictive validity.

7.3.3 Development of an optimum screening instrument to predict clinically significant weight loss

Existing nutritional screening instruments vary in their content. Generally they include anthropometric measurements such as BMI and percentage weight change, as well as aspects of disease status and its impact on nutritional intake or requirements (Stratton *et al*., 2004; Kyle *et al*., 2006). Some also take into account symptom burden such as appetite loss and mood (Vellas *et al*., 1999; Isenring *et al*., 2006). In patients who have cancer, the metabolic consequences of the cachexia

syndrome are also important factors to consider when determining nutritional risk. To date there is no screening instrument which also incorporates this element of the condition.

In Phase II of the present study, exploratory multiple linear regression techniques were used to determine the model which contains the optimum set of variables which could be used to predict clinically significant weight loss over a three month period. Results suggested that when adjusted for age, CASQ items 4 (enjoyment of food) and 12 (pain), along with MUST score and BMI were most predictive of weight change. Interestingly, this model did not include the inflammatory marker C-Reactive Protein which had the strongest correlation with percentage weight change of all the variables tested during the Phase II study. In addition, C-Reactive Protein, when compared with the ability of the CASQ, MUST and MST to predict weight change, was shown to have the highest sensitivity, specificity, NPV and PPV. Furthermore, as supported by previous research, C-Reactive Protein was also found to be an independent predictor of survival (Scott *et al*., 2002; McKernan *et al*., 2008). With the recent proposed definition and diagnostic criteria for the cachexia syndrome (Evans *et al*. 2008), it seems reasonable to suggest that C-Reactive Protein is an important variable to measure when considering the nutritional risk of this group of patients. When compared with the measurement of other markers of the cachexia syndrome, such as TNF-α, IL-1 or IL-6, as a routine and established test, the relative ease of determining a patient's serum C-Reactive Protein concentration in clinical practice should also be considered.

7.3.4 A conceptual model of influences on weight change in people with cancer

The findings from the Phase III qualitative study led to a conceptual model of the processes of the influences on weight change in people with cancer being developed. In addition, Phase II study data has provided further insight into the appetite, symptoms and food intake of this cancer population. From the study data there is also evidence in support of nutritional status being compromised by weight loss in those who experience an increased symptom burden.

What the initial model does not include is the relationship between the cachexia syndrome and change in weight. From the findings of the present study, and understanding of the literature, a revised model (Figure 7.1) demonstrates the proposed interplay between cachexia and the influences on weight change in people with cancer. People with cancer who develop the cachexia syndrome exhibit

a number of symptoms such as fatigue and a reduced appetite which can impact on food intake and hence nutritional status (Inui, 2002). Evidence also exists to support the theory that weight status impacts on treatment outcomes (Andreyev *et al*. 1998). Furthermore, the metabolic effects of the condition, for example the increase in energy requirements, are likely to have a direct influence on weight resulting in a reduction of lean body mass and adipose tissue (Fouladiun *et al*., 2005). This, along with the direct effects of the condition, can impair function and quality of life. The extent to which pre-cachexia directly impacts on symptoms and weight change is not yet understood.

Analysis of the data supports the theory that clinical support should be implemented at every step of the patient's journey and should encompass all elements of the proposed model. This includes addressing the underlying disease and its treatment, the cachexia syndrome and any pre-existing conditions which may be impacting on symptom burden. Nutritional management strategies should be initiated and should provide ongoing support and advice regarding maximisation of nutritional intake. Clinical support should also address issues of self-management and acknowledge the underlying attitudes and beliefs of patients, in addition to aiding and supporting the social support provided by family and caregivers.

Finally, as previously discussed, if the treatment of malnutrition and cachexia is to be successful, interventions must be initiated in a timely manner. The ideal opportunity for this would be in the pre-cachectic stage and/or when the symptoms which impact on food intake are minimal. Current screening instruments, such as the MUST and MST, identify those who are at risk much further down the process, i.e. once food intake has already been impaired. Novel screening initiatives should target the early stages of the disease trajectory.

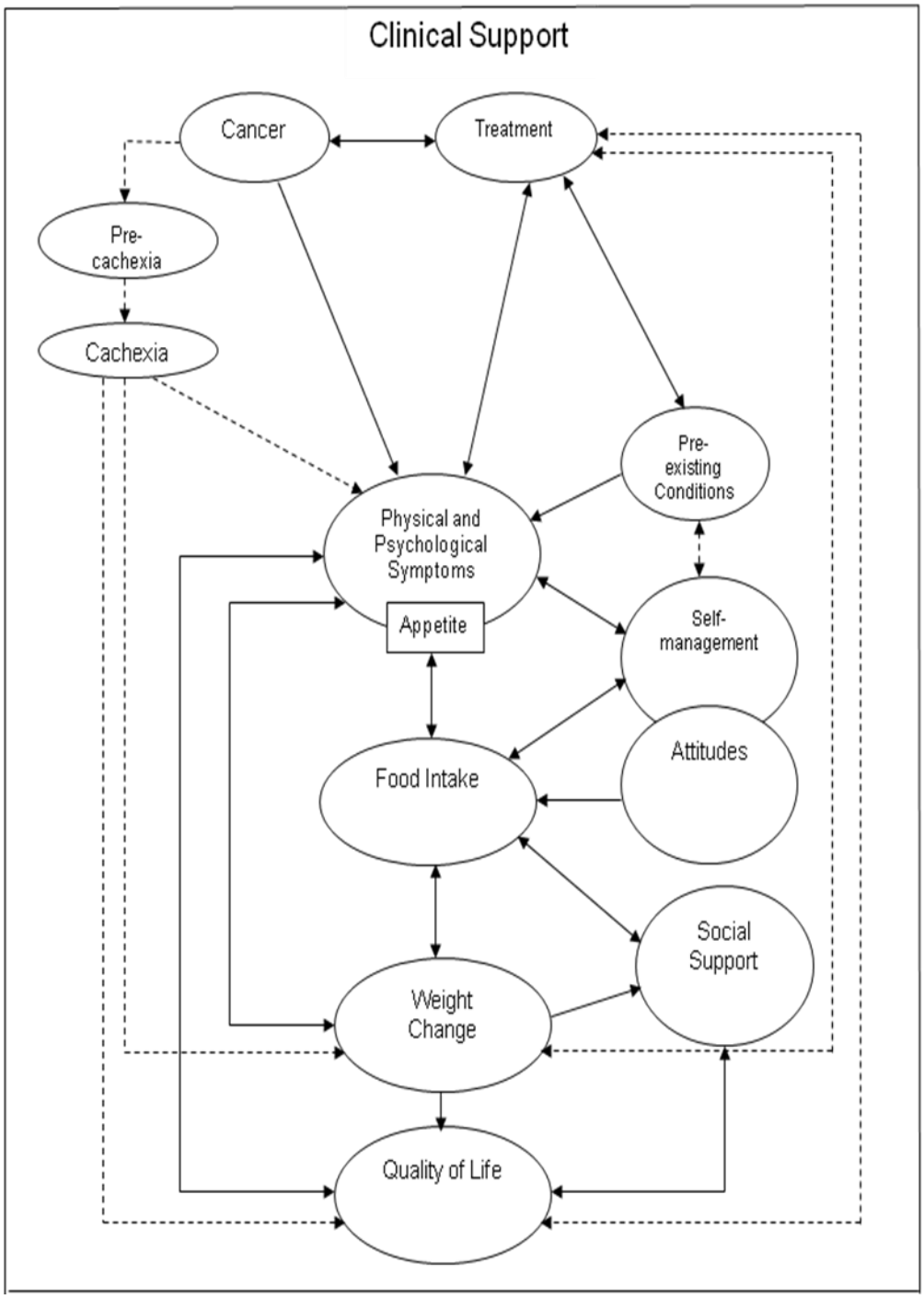

Figure 7.1: Final conceptual model of the process of influences on weight change in people with cancer. Solid line, relationships noted in the Phase III data; dotted line, existing hypotheses.

7.4 Limitations of the study

7.4.1 Phases I and II study sample

As experienced during the current study, the development and validation of any screening instrument is a complex process. Importantly, an instrument only has proven reliability or validity in the population in which it has been tested. In terms of the present study, this means that the reliability of the CASQ has only been ascertained in people with breast, prostate and colorectal cancer who are having radiotherapy. In addition, the instrument's predictive validity has been determined in a different population, i.e. out-patients with lung or upper GI cancer. Furthermore, in the Phase II study population, although there was diversity in terms of age and time since diagnosis, all but one of the participants were white and British. Finally, the initial intention was to determine the predictive validity of the CASQ in a population that was not at high risk of malnutrition. However, the evidence suggests that this was not achieved, as a high proportion of the participants was classed as malnourished by the MST. Rather than being a limitation, this can be viewed as a strength, as the predictive validity of the CASQ has been determined in a more diverse sample in terms of risk of malnutrition. However, despite the inclusion of some patients who were at risk of malnutrition, the performance status of participants and the range of CASQ scores obtained, specifically the limited number of people with very low scores, suggested that the study sample was truncated. All of these factors limit the inferences which can be made about reliability and validity of the CASQ.

7.4.2 Phase II follow-up duration

In the Phase II study, the ability of the CASQ to predict weight loss was determined over a three month follow-up period. This duration was chosen due to the overall poor prognosis of this group of patients, particularly those with lung and pancreatic disease. Consideration must be given to whether the results could have been affected by the length of follow-up. One possibility is that the CASQ has better predictive capabilities over a longer time period. The need to question the follow-up duration is supported by the fact that the follow-up period used when testing the predictive validity of the original eight item CNAQ was six months (Wilson *et al*., 2005). In this study, the sensitivity and specificity of the CNAQ were greater than that of the CASQ.

7.4.3 Phase II sample size

Secondary analysis of the Phase II study data used multiple regression to explore which items of the CASQ, and what other factors, were predictive of weight loss. Although this analysis was only speculative in nature, when interpreting the results consideration must be given to the sample size, more specifically the low number of events, i.e. patients who lost weight, per variable. Less than five events per variable, as was present in this study analysis, could potentially have lead to bias of the regression coefficients and hence bias in the conclusion of the optimum model to predict weight loss (Peduzzi *et al*., 1996). It could also be possible that the relatively low number of patients who lost greater than 5% (n=38) and 10% (n=18) body weight during the study period impacted on the ROC curve analysis, and may have been a contributing factor which resulted in the similar CASQ score cut points for the two different outcomes.

7.4.4 Phase III study

When the Phase III study was designed the intention was to explore the predictors of weight loss in patients with lung and upper GI cancer. Instead, the categories which emerged from the transcript data were focussed around what influenced weight change. This led to some of the findings from the data being similar to the work of Hopkinson *et al.* (2006 and 2007). There were however a number of differences which demonstrate the originality of the current study. For example, the samples studied by Hopkinson *et al.* included only those patients with advanced disease and their carers. Furthermore, the findings of the current study were explored in the context of improving the nutritional care of patients. In contrast, the focus of the work of Hopkinson *et al*. (2006) was helping patients and their families to live with weight loss.

The methods used for sampling Phase III recruits and analysing the data may have led to limitations in the study findings. Although the intention was to use theoretical sampling, due to practical and time constraints, overall the final sample was one of convenience. It did not, for example, include any male spouses or carers. Neither were there any patients with upper GI cancer who were receiving palliative treatment. In addition, following the final interview, although it was felt at the time that no new categories were emerging from the data, a deeper analysis of the data was only conducted later. Therefore, whether true saturation of the data was actually achieved is questionable. Both of these limitations may have resulted in

categories relating to weight change in people with cancer not being discovered and hence, the conceptual model being incomplete.

Finally, one of the strengths of qualitative research is that the data generated can be used to develop theory. On reflection, the qualitative part of this study could have been conducted first and the findings used to inform the development of the CASQ. It is possible that this may have influenced the themes of the items included in the CASQ and may have resulted in an instrument with a more comprehensive coverage of symptoms. Although the instrument was designed with the intention of it being used as a screening tool to predict weight loss within clinical practice, increasing awareness of overall symptom burden is likely to be beneficial.

7.4.5 Researcher reflexivity

Although not a limitation, it is important to reflect on how researcher reflexivity may have contributed to the study findings. Willig (2001) describes two types of reflexivity; personal reflexivity and epistemological reflexivity. Personal reflexivity is the consideration of how the researchers' own beliefs, opinions and experiences may have influenced the construction of meaning from the study findings. In the present study the researcher was a dietitian with over ten years' experience of working within an oncology and palliative care clinical setting. It is important to realise that it is not feasible for the researcher not to bring preconceived beliefs or opinions to this study, particularly regarding what may influence food intake in people with cancer. In addition, there was an existing understanding of the research evidence base surrounding the phenomenon and process of nutritional intake which were explored in this study. Having an awareness of reflexivity certainly helped to prevent existing opinions influencing the construction of meaning and theory from this data. Furthermore, as a novice researcher, undertaking this work has strengthened the understanding of the qualitative research process, in particular, during the analysis stage, the importance of categories emerging from the data rather than from predetermined beliefs.

One aspect of epistemological reflexivity is how the research study design may influence the construction of meaning (Willig, 2001). A point to consider is that the findings from the present study may have been limited by the format of the semi-structured interview questions. For example, the aim was to use open, non-leading questions. However, one of the questions asked if the patient had experienced symptoms and another if they received any advice regarding their eating and

drinking. Inclusion of these questions meant that it was unlikely that symptoms and aspects of support were not going to be present in the data, and hence the model of influences on food intake. A final point to consider is the meaning of what was said by those who were interviewed. From the perspective of the researcher there is the belief that what the interviewees said was their verbal expression of the mental processes surrounding the experiences that they had. It is also important to consider how the presence of the researcher, a dietitian, may have influenced what the participants disclosed, for example, when discussing issues of healthy eating.

7.5 Comments on the research process

In addition to the implications for clinical practice, it is important to acknowledge what has been learnt regarding the research process. The challenges of recruiting patients, particularly those receiving palliative care, into research studies have been previously reported in the literature (Ewing *et al*., 2004; O'Mara *et al*., 2009). Indeed, recruitment to the present study was found to be challenging. Despite there being no intervention and the participant research burden being comparatively low for this study, some of those approached felt unable to participate. Reasons given for refusal were related to 'having too much to cope with' or being unable to read the participant information sheet due to not having spectacles with them. Others who had received curative treatment felt that it was inappropriate to be given an information sheet with a title of 'predicting weight loss in cancer'. It is important to consider that patients diagnosed with cancer are likely to receive a plethora of information, particularly around the time of diagnosis. Some may be unable to deal with the additional burden of participating in a research study. In addition, a proportion of the U.K. population has low literacy levels (National Literacy Trust, 2009) and for some people, the request to read several pages of study information may be daunting. Several potential participants commented on the length of the information sheet for what they deemed to be a study that involved filling in a questionnaire. In particular, the section entitled 'What if something goes wrong' led them to think that they had missed something that they would need to do. Issues such as these need to be addressed sensitively by the researcher, ensuring that patients feel informed, but not pressurised to participate. Further consideration to the format of participant information sheets and the wording may also be beneficial.

Recruitment of participants to this study was extremely time consuming and took longer than predicted. The most effective way was for the researcher to attend the out-patient clinics. This is a method that has been found to be successful by others

(O'Mara *et al*., 2009). Simply screening notes and visiting the clinic to see ad-hoc patients resulted in potential participants being missed as inevitably clinics did not run to time. In addition, relying on busy clinic staff to be involved in the recruitment process proved to be ineffective. As a dietitian working in a clinical research setting it is favourable to work alongside an established multi-professional research team. This not only provides a source of knowledge and experience but also enables the challenges of research to be conducted in a supportive environment. Finally, to ensure recruitment of a diverse sample, in addition to assisting recruitment rates, a multi-centred collaboration may prove to be beneficial.

7.6 Implications for practice and future research

The dietetic profession is a practice-based discipline and, as in all areas of healthcare, a sound research evidence base is paramount to ensure the health and wellbeing of service users as well as maintaining the credibility of the profession. The evidence base is derived from research which is used as a tool to both develop and test theories. In the present study, Phases I and II involved the testing of the hypothesis that 'a simple and practical screening instrument, with demonstrated reliability and validity, can predict clinically significant weight loss in people with lung or upper GI cancer'. Results from the two studies allow us to accept this hypothesis. However, for the reasons previously discussed, implementation of the CASQ into the clinical setting is not appropriate. For this reason, no implications in terms of changing clinical practice have evolved from the testing of this hypothesis. Nonetheless, as will be discussed in the following section, from the three phases of the study, new substantive theories have emerged related to the further development of a screening instrument to predict weight loss, evaluation of symptoms and the influences on weight change in people with cancer. Conducting further research will enable these theories to be tested, following which they may become generalisable. In particular, the model developed from the Phase III study provides insight into the processes involved regarding nutritional concerns of the individual and the way that they self-manage their condition. For dietitians or any healthcare professionals, this improved understanding may enable a more holistic approach when assessing, treating and monitoring the care provided to service users.

7.6.1 Predicting weight loss screening instrument

Further research is required to develop a screening instrument which is able to predict clinically significant weight loss in the cancer population. Following multiple linear regression techniques with the Phase II study data, two models were proposed. The first included CASQ items six (snacks), nine (nausea) and 12 (pain). If the purpose of the intended instrument is solely to predict weight loss then further testing of this model may be warranted. However, completion of a tool with these particular items would give little evaluation of symptoms. In addition, it is interesting that this model does not directly include any item relating to appetite. The second proposed model included CASQ items four (enjoyment of food) and 12 (pain), MUST score, BMI and age. A model such as this could have a dual purpose of screening for malnutrition and predicting weight loss (Appendix 30). For example, establishing the patient's MUST score, which includes calculation of BMI, would identify those patients who were at risk from malnutrition. This data, along with age and responses to CASQ items four and 12 could then be used to determine their risk of future weight loss. It is possible that the themes of these two items have the greatest influence on food intake and hence weight status. As seen in the Phase III study data, enjoyment of food emerged as an important aspect in the feeding process. Pain was also identified from the qualitative data as influencing food intake as well as overall sense of wellbeing. The prospective validity testing of a model such as this would need to be conducted with a diverse sample of patients with cancer. Furthermore, research would need to focus on the scoring of the item responses and, as discussed below, the nutritional intervention point following MUST screening.

Overall, the results from the Phase II study also suggested that a third option of testing C-Reactive Protein as a predictor of weight loss is warranted. In clinical practice the usual reference range for serum C-Reactive Protein concentration is 0 to 10mg/L. Findings from this study suggested that serum concentrations of >15mg/L may be predictive of weight loss. Further prospective testing with a larger sample size of patients with cancer would need to be conducted to establish the optimum cut-point for C-Reactive Protein. In clinical practice C-Reactive Protein is not always routinely analysed, therefore there would be practical and financial issues of implementing this aspect of screening. As our understanding of the cachexia syndrome improves, and with a worldwide consensus definition hopefully imminent, research should also focus on the screening of patients with the syndrome or, ideally, those in a pre-cachectic state. It is probable that C-Reactive

Protein would be included in such a tool. A validated instrument will enable therapies to be commenced as early as possible in the disease trajectory with the hope of stabilising, if not improving, function and quality of life.

7.6.2 Screening for malnutrition

The British Dietetic Association and the National Institute for Health and Clinical Excellence both support the use of the MUST in clinical practice (NICE, 2006; BDA, 2009). However, a critical review of the literature showed that the usefulness of the MUST in identifying those at risk of malnutrition remains uncertain in patients with cancer. Findings from this Phase II study following multiple linear regression techniques suggest that, when adjusted for all other variables, a MUST score of one remained an independent predictor of weight loss. This implies that in groups of out-patients with lung or upper GI cancer, being identified at moderate risk from malnutrition may warrant nutritional intervention. Further testing of the MUST throughout the cancer population, using a cut off of ≥ 1 as an intervention point, is now needed. Dietetic services that are struggling to cope with the current workload demands will find an increase in referral rates from those being identified by the MUST as being at moderate, as opposed to high risk, a challenge. That said, consideration needs to be given to the advantages of providing dietary intervention at an earlier stage in the disease trajectory.

7.6.3 Evaluation of symptoms

The importance of identifying symptoms which influence food intake was evident from Phase III of the study. In addition to being able to predict weight loss, the CASQ could also be used within clinical practice to evaluate patients' symptoms. This may be as part of the initial assessment process, or following implementation of treatment. From the integration of the findings from Phase III of the present study with the existing CASQ, a 16-item tool for the evaluation of appetite and symptoms for use in people with cancer, has been proposed (Appendix 31). Phase III study findings suggested that items one (appetite), two (satiety), three (hunger) and four (enjoyment of food) provided important information on the four elements of the feeding process, i.e. the physiological sensations of hunger, the desire to eat, enjoyment of eating, and feelings of satiety. It was therefore considered important to include these items in the proposed evaluation tool. However, from the qualitative data, the subjectivity of appetite was emphasised, with patients comparing their current state to what they deemed normal. In an attempt to improve the clarity and meaning of item one (appetite), it has been proposed that it be reworded to include

the words ‘desire to eat’. Indirectly, CASQ items five (number of meals) and six (number of snacks) may provide information on appetite. However, during Phase II of the study, patients were often unsure of what defined a meal and a snack suggesting that the wording was ambiguous. In addition, if the tool is to evaluate appetite and symptoms, it is questionable whether items five and six relating to the number of meals and snacks eaten are necessary. On this basis, these two items have not been included in the proposed evaluation tool. The six remaining items of the CASQ relating to nausea and vomiting, taste, mood, energy levels and pain were all symptoms experienced by the Phase III study sample, signifying that they were indeed relevant and should be included in the proposed tool. However, as respondents during Phase II of the study were unsure of the difference between the two items relating to taste only CASQ item eight (taste changes) has been included. Furthermore, guided by the qualitative data analysis, in its current form the range of symptoms covered by the CASQ is not exhaustive. It has therefore been proposed that new items are included on the subject of weight loss, indigestion, sore mouth/throat, vomiting, constipation, diarrhoea and anxiety. Finally, a question has been added to capture any additional symptoms that patients may be experiencing. The proposed tool would need to be tested prospectively within the cancer population before being implemented into clinical practice.

7.6.4 Self-monitoring of weight

Findings from the Phase III study suggest that self-monitoring of weight is something that patients with cancer routinely do. This technique has been used to assist weight loss in the obese but is not something that has previously been reported in the literature to promote stabilisation or weight gain in the cancer population. Further research to investigate the optimum frequency of self-monitoring of weight in people with cancer may be able to positively influence motivation to eat or compliance with dietary treatment, and hence weight status.

7.6.5 Influence of body image on compliance to dietetic treatment

Another area for further research is in relation to the influence of perceived body image on compliance to treatment. Findings from the qualitative data, which are previously unreported in the literature, suggest that some people initially may be pleased with losing weight as this leads to an improved body image. As a dietitian providing nutritional support to patients with cancer, acknowledgement of this as a potential barrier to compliance is important. Further research in this area may help to establish whether this phenomenon is established throughout the cancer

population, if age or gender influence perceptions and what the best management strategies may be.

7.6.6 The ‘healthy eating’ conflict

In an era where the messages of healthy eating and ‘five a day’ are well-heard mantras, findings from the qualitative data suggest that adherence to these guidelines remains important for patients with cancer, their family and carers. Being unable to eat healthy foods such as fruit and vegetables was an obvious concern for patients and their carers. Further exploration and understanding of these beliefs may help improve the type and quality of the dietary advice which is offered with a view to assisting patient compliance.

7.7 Final conclusion

In conclusion, the findings from this study have provided a deeper understanding of the complex factors that have an effect on, and can predict, weight change in people with cancer. The results from the psychometric testing of the Cancer Appetite and Symptom Questionnaire imply that the hypothesis that ‘a simple and practical screening instrument, with demonstrated reliability and validity, can predict clinically significant weight loss in people with lung or upper GI cancer’ can be accepted. However, further developmental work and testing needs to be conducted before it is appropriate for use in clinical practice. From this study arises an increase in awareness of the individual and complex social processes which surround the issues of food intake and weight management in people with cancer. This knowledge can inform dietitians and healthcare professionals, influence their nutritional management strategies, with the hope of providing more holistic care and an enhanced experience for service users.

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Council on Nutrition Appetite Questionnaire (CNAQ)

Name:_____Sex (circle): Male Female
Age:_____Weight:_____Height:_____
Date:_____

Administration Instructions: Ask the subject to complete the questionnaire by circling the correct answers and then tally the results based upon the following numerical scale: a = 1, b = 2, c = 3, d = 4, e = 5. The sum of the scores for the individual items constitutes the CNAQ score. CNAQ score ≤ 28 indicates significant risk of at least 5% weight loss within six months.

1. My appetite is
a) Very poor
b) poor
c) average
d) good
e) very good

2. When I eat
a) I feel full after eating only a few mouthfuls
b) I feel full after eating about a third of a meal
c) I feel full after eating over half a meal
d) I hardly ever feel full

3. I feel hungry
a) rarely
b) occasionally
c) some of the time
d) most of the time
e) all of the time

4. Food tastes
a) very bad
b) bad
c) average
d) good
e) very good

5. Compared to when I was younger food tastes
a) much worse
b) worse
c) just as good
d) better
e) much better

6. Normally I eat

a) less than one meal a day
b) one meal a day
c) two meals a day
d) three meals a day
e) more than three meals a day

7. I feel sick or nauseated when I eat

a) most times
b) often
c) sometimes
d) rarely
e) never

8. Most of the time my mood is

a) very sad
b) sad
c) neither sad nor happy
d) happy
e) very happy

Simplified Nutritional Appetite Questionnaire (SNAQ)

Name:_____Sex (circle): Male Female
Age:_____Weight:_____Height:_____
Date:_____

Administration Instructions: Ask the subject to complete the questionnaire by circling the correct answers and then tally the results based upon the following numerical scale: a = 1, b = 2, c = 3, d = 4, e = 5. The sum of the scores for the individual items constitutes the SNAQ score. SNAQ score ≤ 14 indicates significant risk of at least 5% weight loss within six months.

1. My appetite is
f) Very poor
g) poor
h) average
i) good
j) very good

2. When I eat
a) I feel full after eating only a few mouthfuls
b) I feel full after eating about a third of a meal
c) I feel full after eating over half a meal
d) I hardly ever feel full

3. Food tastes
f) very bad
g) bad
h) average
i) good
j) very good

4. Normally I eat
e) less than one meal a day
f) one meal a day
g) two meals a day
h) three meals a day
e) more than three meals a day

Cancer Appetite and Symptom Questionnaire

Please tick the box that most closely reflects your experiences with appetite and symptoms at the present time.

1. My appetite is…
- ☐ very poor
- ☐ poor
- ☐ average
- ☐ good
- ☐ very good

2. When I eat I feel full…
- ☐ without having eaten anything
- ☐ after eating only a few mouthfuls
- ☐ after eating about a third of a meal
- ☐ after eating over half a meal
- ☐ after eating a full meal

3. Before eating, I feel hungry…
- ☐ rarely
- ☐ occasionally
- ☐ some of the time
- ☐ most of the time
- ☐ all of the time

4. I enjoy the food I do eat…
- ☐ most times
- ☐ often
- ☐ sometimes
- ☐ rarely
- ☐ never

5. At present I eat…
- ☐ less than one meal a day
- ☐ one meal a day
- ☐ two meals a day
- ☐ three meals a day
- ☐ more than three meals a day

6. At present I eat (in addition to or instead of meals)…
- ☐ no snacks
- ☐ one snack a day
- ☐ two snacks a day
- ☐ three snacks a day
- ☐ four or more snacks a day

7. Compared to before I was ill, food tastes…
- ☐ much worse
- ☐ worse
- ☐ just as good
- ☐ better
- ☐ much better

8. At present I have…
- ☐ no changes in taste
- ☐ mild taste changes
- ☐ moderate taste changes
- ☐ severe taste changes
- ☐ no taste at all

9. I feel sick or nauseated before I eat or when I eat…
- ☐ most times
- ☐ often
- ☐ sometimes
- ☐ rarely
- ☐ never

10. Most of the time my mood is…
- ☐ very sad
- ☐ sad
- ☐ neither sad nor happy
- ☐ happy
- ☐ very happy

11. Most of the time my energy level is…
- ☐ very high
- ☐ high
- ☐ moderate
- ☐ low
- ☐ very low

12. Most of the time my pain is…
- ☐ very mild or no pain
- ☐ mild
- ☐ moderate
- ☐ severe
- ☐ very severe

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.
Please fill in your initials:
Your birth date (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4

19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

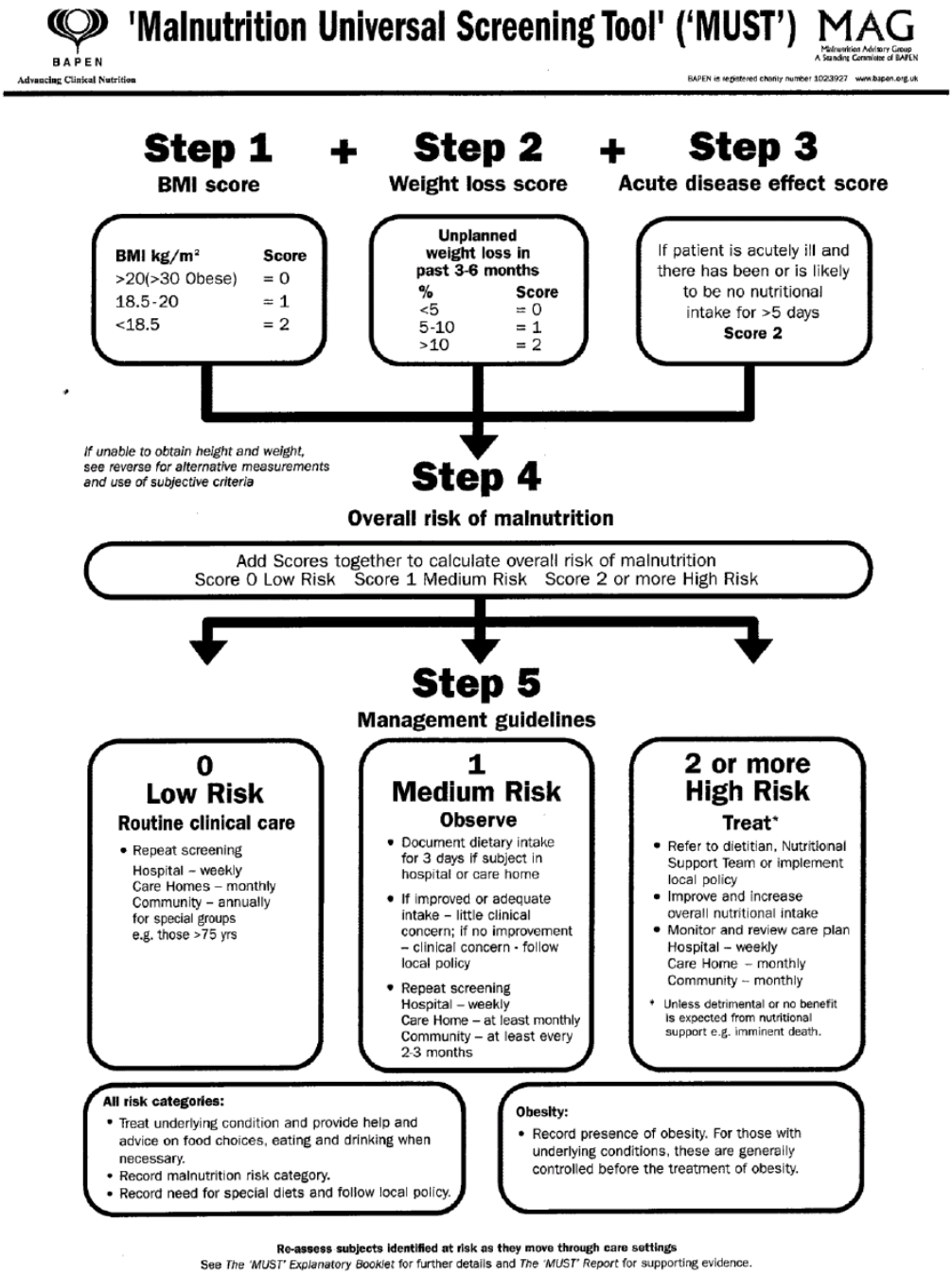
Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

Appendix 5: Malnutrition Universal Screening Tool (MUST)



Subjective global assessment (SGA)
(Select appropriate category with a checkmark, or enter numerical value where indicated by "#.")

A. History
1. Weight change
Overall loss in past 6 months: amount = # _____ kg; % loss = # _____
Change in past 2 weeks: _____ increase,
_____ no change,
_____ decrease.

2. Dietary intake change (relative to normal)
_____No change,
_____Change _____duration = # _____ weeks
_____type: _____ suboptimal liquid diet, _____ full liquid diet
_____ hypocaloric liquids, _____ starvation.

3. Gastrointestinal symptoms (that persisted for >2 weeks)
_____none, _____nausea, _____vomiting, _____diarrhoea, _____anorexia.

4. Functional capacity
_____ No dysfunction (e.g., full capacity),
_____ Dysfunction _____ duration = # _____weeks.
_____ type: _____working suboptimally,
_____ambulatory,
_____bedridden.

5. Disease and its relation to nutritional requirements
Primary diagnosis (specify) _____
Metabolic demand (stress) : _____ no stress,_____low stress,
_____moderate stress, _____high stress.

B. Physical (for each trait specify: 0 = normal, 1+ = mild, 2+ = moderate, 3+ = severe).
_____loss of subcutaneous fat (triceps, chest)
_____muscle wasting (quadriceps, deltoids)
_____ankle edema
_____sacral edema
_____ascites

C. SGA rating (select one)
_____ A = Well nourished
_____ B = Moderately (or suspected of being) malnourished
_____ C = Severely malnourished

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

History (Boxes 1-4 are designed to be completed by the patient.)

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____ pounds
I am about _____ feet _____ tall

One month ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds

During the past two weeks my weight has:
☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1 ☐

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:
☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)
I am now taking:
☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritonal supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0)

Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):
☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ vomiting (3)
☐ constipation (1)
☐ diarrhea (3)
☐ mouth sores (2)
☐ dry mouth (1)
☐ things taste funny or have no taste (1)
☐ smells bother me (1)
☐ problems swallowing (2)
☐ feel full quickly (1)
☐ pain; where? (3)_____
☐ other** (1) _____

** Examples: depression, money, or dental problems

Box 3 ☐

4. Activities and Function: Over the past month, I would generally rate my activity as:
☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bedridden, rarely out of bed (3)

Box 4 ☐

Additive Score of the Boxes 1-4 ☐ A

The remainder of this form will be completed by your doctor, nurse, or therapist. Thank you.

5. Disease and its relation to nutritional requirements *(See Worksheet 2)*

All relevant diagnoses (specify) _____

Primary disease stage (circle if known or appropriate) I II III IV Other _____

Age _____

Numerical score from Worksheet 2 ☐ B

6. Metabolic Demand *(See Worksheet 3)*

Numerical score from Worksheet 3 ☐ C

7. Physical *(See Worksheet 4)*

Numerical score from Worksheet 4 ☐ D

Global Assessment *(See Worksheet 5)*
☐ Well-nourished or anabolic (SGA-A)
☐ Moderate or suspected malnutrition (SGA-B)
☐ Severely malnourished (SGA-C)

Total PG-SGA score
(Total numerical score of A+B+C+D above) ☐
(See triage recommendations below)

Clinician Signature _____ RD RN PA MD DO Other __ Date _____

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

0-1	No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3	Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and laboratory values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms survey (Box 3).
≥ 9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

Appendix 8: Abridged Patient Generated Subjective Global Assessment (ab-PG-SGA)

Abridged Patient-Generated Subjective Global Assessment (PG-SGA)

Please complete the following

Patient ID:

1. Weight

In summary of my current and recent weight:

I currently weigh about _____

I am about _____ tall

One month ago I weighed about _____

Six months ago I weighed about _____

During the past two weeks my weight has:

☐ Decreased ☐ Not changed ☐ Increased

2. Food Intake

As compared with my normal intake, I would rate my food intake during the past month as:

☐ Unchanged ☐ More than usual ☐ Less than usual

I am now taking:

☐ Normal food, but less than normal amount
☐ Little solid food
☐ Only liquids
☐ Only nutritional supplements
☐ Very little of anything
☐ Only tube feedings or nutrition by vein

3. Symptoms

I have had the following problems that have kept me from eating enough during the past two weeks (tick all that apply):

☐ No problem eating
☐ No appetite, did not feel like eating
☐ Constipation
☐ Mouth sores
☐ Food tasting funny / having no taste
☐ Pain: where? _____
☐ Other* _____

☐ Vomiting
☐ Nausea
☐ Diarrhoea
☐ Dry mouth
☐ Smells bother me
☐ Problems swallowing
☐ Feeling full quickly

4. Activities and Function

Over the past month, I would generally rate my activity as (please tick only one box):

☐ Normal with no limitations *(no action required)*
☐ Not my normal, but able to be up and about with fairly normal activities
☐ Not feeling up to most things, but in bed or chair for less than half of the day
☐ Able to do little activity and spend most of the day in bed or chair
☐ Pretty much bedridden, rarely out of bed

Malnutrition Screening Tool (MST)

Question		Score
Have you lost weight without trying?		
No		0
Unsure	2	
Yes		See below
If yes, how much weight (kg) have you lost?		
1-5		1
6-10		2
11-15		3
>15		4
Unsure	2	
Have you been eating poorly because of a decreased appetite?		
No		0
Yes		1

Total score =

_____

Score of two or more = patient at risk of malnutrition

Mini Nutritional Assessment
MNA®

Complete the screen by filling in the boxes with the appropriate numbers. Total the numbers for the final screening score.

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake

B Weight loss during the last 3 months
0 = weight loss greater than 3 kg (6.6 lbs)
1 = does not know
2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs)
3 = no weight loss

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems

F1 Body Mass Index (BMI) (weight in kg) / (height in m^2)
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater

IF BMI IS NOT AVAILABLE, REPLACE QUESTION F1 WITH QUESTION F2.
DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.

F2 Calf circumference (CC) in cm
0 = CC less than 31
3 = CC 31 or greater

Screening score
(max. 14 points)

12-14 points: Normal nutritional status
8-11 points: At risk of malnutrition
0-7 points: Malnourished

Nutritional Risk Screening (NRS 2002)

Table 1 Initial screening			
1	Is BMI <20.5?	Yes	No
2	Has the patient lost weight within the last 3 months?		
3	Has the patient had a reduced dietary intake in the last week?		
4	Is the patient severely ill ? (e.g. in intensive therapy)		
Yes: If the answer is 'Yes' to any question, the screening in Table 2 is performed. **No**: If the answer is 'No' to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			

Table 2 Final screening			
	Impaired nutritional status	**Severity of disease (≈ increase in requirements)**	
Absent **Score 0**	Normal nutritional status	Absent **Score 0**	Normal nutritional requirements
Mild **Score 1**	Wt loss >5% in 3 mths or Food intake below 50–75% of normal requirement in preceding week	Mild **Score 1**	Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*. *Chronic hemodialysis, diabetes, oncology*
Moderate **Score 2**	Wt loss >5% in 2 mths or BMI 18.5–20.5 + impaired general condition or Food intake 25–60% of normal requirement in preceding week	Moderate **Score 2**	Major abdominal surgery* Stroke* *Severe pneumonia, hematologic malignancy*
Severe **Score 3**	Wt loss >5% in 1 mth (>15% in 3 mths) or BMI <18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week in preceding week.	Severe **Score 3**	Head injury* Bone marrow transplantation* *Intensive care patients (APACHE>10).*
Score:	+	**Score:**	**=Total score**
Age	if ≥70 years: add 1 to total score above	**=age-adjusted total score**	
Score ≥3: the patient is nutritionally at-risk and a nutritional care plan is initiated **Score <3**: weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			

NRS-2002 is based on an interpre-tation of available randomized clinical trials.
*indicates that a trial directly supports the categorization of patients with that diagnosis. Diagnoses shown in *italics* are based on the prototypes given below.
Nutritional risk is defined by the present **nutritional status** and risk of impairment of present status, due to **increased requirements** caused by stress metabolism of the clinical condition.

A nutritional care plan is indicated in all patients who are

(1) severely undernourished (score = 3), or (2) severely ill (score = 3), or (3) moderately undernourished + mildly ill (score 2 + 1), or (4) mildly undernourished + moderately ill (score 1 + 2).

Prototypes for severity of disease
Score = 1: a patient with chronic disease, admitted to hospital due to complications. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases.
Score = 2: a patient confined to bed due to illness, e.g. following major abdominal surgery. Protein requirement is substantially increased, but can be covered, although artificial feeding is required in many cases.
Score = 3: a patient in intensive care with assisted ventilation etc. Protein requirement is increased and cannot be covered even by artificial feeding. Protein breakdown and nitrogen loss can be significantly attenuated.

Appendix 12: Glasgow Prognostic Score (GPS)

Glasgow Prognostic Score (GPS)

C-Reactive Protein >10mg/L score = 1
C-Reactive Protein <10mg/L score = 0

Albumin <35g/L score = 1
Albumin >35g/L score = 0

Total score =

The Prognostic Inflammatory Nutritional Index (PINI)

PINI = [alpha 1-acid glycoprotein (AAG) x C-reactive protein (CRP)] divided by [albumin x prealbumin])

The prognostic value of the score is as follows: >30 = life risk, 21-30 = high risk, 11-20 = medium risk, 1-10 = low risk and <1 = minimal risk; normal, healthy individual

FAACT (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicated how true each statement has been for you during the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy.....	0	1	2	3	4
GP2	I have nausea.....	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
GP4	I have pain.....	0	1	2	3	4
GP5	I feel bothered by side effects of treatment.....	0	1	2	3	4
GP6	I feel ill.....	0	1	2	3	4
GP7	I am forced to spend time in bed.....	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family.....	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness.....	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.					
GS7	I am happy with my sex life.....	0	1	2	3	4

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad.....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope with the fight against my illness	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am unable to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well.....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C6	I have a good appetite.....	0	1	2	3	4
ACT1	The amount I eat is sufficient to meet my needs.	0	1	2	3	4
ACT 2	I am worried about my weight.....	0	1	2	3	4
ACT 3	Most food tastes unpleasant to me.....	0	1	2	3	4
ACT 4	I am concerned about how thin I look.....	0	1	2	3	4
ACT 6	My interest in food drops as soon as I start to eat	0	1	2	3	4
ACT7	I have difficulty eating rich or 'heavy' foods.....	0	1	2	3	4
ACT9	My family and friends are pressuring me to eat...	0	1	2	3	4
O2	I have been vomiting.....	0	1	2	3	4
ACT10	When I eat, I seem to get full quickly.....	0	1	2	3	4
ACT11	I have pain in my stomach area.....	0	1	2	3	4
ACT13	My general health is improving.....	0	1	2	3	4

Nottingham University Hospitals NHS
NHS Trust

Predicting weight loss in people with cancer: Development of a screening tool (Phase I)

Patient Information Sheet

Please read this information carefully and feel free to ask any questions or to request further information.

Investigators: Vanessa Siddall (Research Dietitian)
Dr. Andrew Wilcock (Reader/Consultant in Palliative Medicine)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. You should take time, at least 24 hours, to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

Many people with cancer will experience a reduced appetite and weight loss. This is associated with symptoms of muscle weakness, fatigue and altered mood, which can interfere with activities of daily living. These symptoms can be difficult to treat but we know that providing advice about food and diet to people as early as possible can help.

This study will look at the development of a questionnaire which can be used to identify those people who are most at risk of losing weight.

Why have I been invited to participate?

You have been chosen because you are attending a radiotherapy department for treatment for cancer.

Do I have to take part?

You are under no obligation at all to take part in this study. It is up to you to decide whether or not you take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form, which you will be given a copy of. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision

not to take part, will not affect the standard of care you receive either at home or in hospital.

What will happen to me if I take part?

The study involves completing a short questionnaire about appetite and symptoms. Completing the questionnaire should take about 5 minutes. You need to fill in the questionnaire on two separate occasions one week apart. This can be done during your visits to the radiotherapy department. No additional visits to the hospital will be necessary.

What are the side effects of taking part?

There are no side effects from taking part.

What are the possible disadvantages and risks of taking part?

We do not believe that there are any disadvantages of taking part other than providing approximately10 minutes of your time.

What are the possible benefits of taking part?

There are no direct benefits to you by taking part in this study but by taking part you are helping to develop our knowledge of the best ways of improving services given to people with cancer.

What if something goes wrong?

If taking part in this research harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds for legal action but as in other cases in civil law you would need to employ a lawyer and pay for their services in the usual way. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, you may wish to contact the Trust's Patient Advice and Liaison Service (PALS), Hospital Headquarters, Nottingham City Hospital, FREEPOST MID21426, Nottingham, NG5 1BR. Tel: 0800 0521195.

Will my taking part in this study be kept confidential?

All information that is collected about you during the study will be kept strictly confidential. With your consent, we would inform your GP of your participation. The information that you provide will be entered onto a database controlled by the research team. The data will be entered onto the database in an anonymised form

(e.g. you will be identified by a number not by your name). Access to the database containing the data is restricted to authorised personnel and is password protected.

What will happen to the results of the research study?

This study is being undertaken as part of a PhD educational qualification and the study results will be used to write a report as part of this qualification. Results from the study will be published in medical journals and presented at national and international research meetings. You will not be referred to by name or be identified in any presentation or report of the study results. If you withdraw your consent to participate in the study, no new data will be collected or processed. However, you may be asked to agree to some of the data already collected about you being used. During this study, you have the right to access the data relating to your taking part in the study, and, in the event of any inaccuracies about you being recorded in the study data, you have the right to request that such data be corrected. Please talk to the research team about this.

Who is organising and funding the research?

The study is co-ordinated by Ms.Vanessa Siddall and Dr Wilcock at the University of Nottingham. It is funded by The National Cancer Research Institute.

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your safety, rights, welfare and dignity. This study has been reviewed and given a favourable opinion by the Derbyshire Research Ethics Committee.

Contact for further information

Please keep this sheet to think about the study and to discuss with your family or friends. We will happily see you and your relatives or friends together to answer any questions about the study.

Whilst on the study, if you (or your own family doctor) have any additional questions, please contact one of the research team on 0115 962 7619.

Ms. Vanessa Siddall	- Research Dietitian
Dr Andrew Wilcock	- Reader/Consultant
Sr Cathann Manderson	- Research Sister
Dr Dough Hooper	- Research Specialist Registrar

Appendix 16: Phase I consent form

Nottingham University Hospitals NHS
NHS Trust

Study Number: 07/H0401/92
Patient study identification number:

Consent Form

Title of Project: **Predicting weight loss in people with cancer: Development of a screening tool. (Phase I)**

Investigators: **Dr Andrew Wilcock (Reader/Consultant in Palliative Medicine and Oncology)**
Ms Vanessa Siddall (Research Dietitian)

The patient should complete the whole of this sheet himself/herself.

Please initial box

1. I confirm that I have read and understood the patient information sheet version 1.2 dated July 2007 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my G.P being informed about my participation in the study. ☐
5. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of Person taking consent (If different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes.

Eastern Cooperative Oncology Group (ECOG) Performance status

Grade	Scale
0	Fully active, able to carry out all predisease activity without restriction.
1	Restricted in physically strenuous activity, but not ambulatory and able to carry out work of a light or sedentary nature eg. light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.

Nottingham University Hospitals NHS
NHS Trust

Dear

In 2006 the National Institute for Health and Clinical Excellence (NICE), an organisation responsible for providing national guidance on the prevention and treatment of health problems, made a recommendation that all hospital outpatients should be screened to identify those at risk of malnutrition and weight loss.

Here at Nottingham University Hospitals NHS Trust we would like to put into practice the screening process in our outpatient clinics. The screening process involves having your height and weight measured by a member of staff and telling us if for any reason you have not been able to eat or drink for the last 5 days. If you do not wish to be included in the screening process please let a member of the clinic staff know.

As well as putting into practice the screening process our hospital research team is looking for people to take part in a study who have **not** lost a large amount of weight over the past three to six months.

If you are eligible and interested in taking part a member of our research team will speak to you at your clinic visit to discuss the study.

Yours faithfully,

Consultant Physician

Nottingham University Hospitals NHS
NHS Trust

Predicting weight loss in people with cancer: Development of a screening tool

Patient Information Sheet

Please read this information carefully and feel free to ask any questions or to request further information.

Investigators: Vanessa Siddall(Research Dietitian)
Dr Andrew Wilcock (Reader/Consultant in Palliative Medicine)

You are being invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. You should take time reading this and deciding whether or not you would wish to take part. If you do not feel able to make a decision today but over the next 2 to 3 days decide that you would like to take part in the study please contact a member of the research team on the telephone number below so that it can be arranged. Thank you for reading this.

What is the purpose of the study?

Many people with cancer will experience a reduced appetite and weight loss. This is associated with symptoms of muscle weakness, tiredness and altered mood, which can interfere with activities of daily living. These symptoms can be difficult to treat

but we know that providing advice about food and diet to people as early as possible can help.

This study will look at how certain measurements and a questionnaire can be used to identify those people who are most at risk of losing weight. It will also ask people with cancer and their partners or carers about their experience of losing weight and any information that they have received about food and diet. From this we may be able to decide on the best way to help people with cancer maintain their weight.

Why have I been invited to participate?

You have been chosen because of your diagnosis of cancer and your weight has not changed by a significant amount.

Do I have to take part?

You are under no obligation at all to take part in this study. It is up to you to decide whether or not you take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form, which you will be given a copy of. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive either at home or in hospital.

What will happen to me if I take part?

The study involves completing a short questionnaire about appetite and symptoms. Completing the questionnaire should take about 5 minutes. We would also like you to have a blood sample taken (2 teaspoons of blood). If you have already had a blood test today, with your permission, we will use this sample. Alternatively, if you feel able, we can arrange for a blood sample to be taken from you at the clinic visit today.

A member of the research team will write down information about your diagnosis, treatment, weight and any previous weight loss and activity level.

In three months time you will need to be weighed again. If you are due to come to the clinic in three months time a member of the research team or clinic staff will record your weight there. If you do not have an out patient appointment in three months time a member of the research team can visit you at home. Alternatively you

can choose to attend and be weighed at Hayward House at Nottingham City Hospital which ever is most convenient for you.

At the end of the study we will interview up to 20 of the people that have lost weight over the three month period. You may be invited to be interviewed and if you have a partner or carer they will also be asked if they want to take part. It will involve answering questions and talking to a researcher about your appetite, weight and any advice and support that you have received about food and diet. You will be given the option to be interviewed at home or at the hospital. The interview should not last longer than one hour. To help us analyse the results the session will be tape recorded.

In the event of an additional hospital visit being required for either parts of the study, reasonable travel expenses will be reimbursed.

If you would like to take part in the first part of the study but do not wish to be interviewed please tell us.

What are the side effects of taking part?

There are no side effects from taking part. For some people talking about their diagnosis and treatment may raise some emotional issues.

What are the possible disadvantages and risks of taking part?

We do not believe that there are any disadvantages of taking part other than providing approximately 10 to 20 minutes of your time today and approximately 10 minutes in three months time.

If you are interviewed this would take up to an hour of your time.

What are the possible benefits of taking part?

There are no direct benefits to you by taking part in this study but by taking part you are helping us to develop our knowledge of the best ways of improving services given to people with cancer.

What if something goes wrong?

If taking part in this research harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds for legal action but

as in other cases in civil law you would need to employ a lawyer and pay for their services in the usual way. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, you may wish to contact the Trust's Patient Advice and Liaison Service (PALS), Hospital Headquarters, Nottingham City Hospital, FREEPOST MID21426, Nottingham, NG5 1BR.

Will my taking part in this study be kept confidential?

All information that is collected about you during the study will be kept strictly confidential. With your consent, we would inform your GP of your participation. The information that you provide will be entered onto a database controlled by the research team. The data will be entered onto the database in an anonymised form (e.g. you will be identified by a number not by your name). Access to the database containing the data is restricted to authorised personnel and is password protected.

What will happen to the results of the research study?

This study is being undertaken as part of a PhD educational qualification and the study results will be used to write a report as part of this qualification.

Results from the study will be published in medical journals and presented at national and international research meetings. You will not be referred to by name or be identified in any presentation or report of the study results. If you withdraw your consent to participate in the study, no new data will be collected or processed. However, you may be asked to agree to some of the data already collected about you being used.

During this study, you have the right to access the data relating to your taking part in the study, and, in the event of any inaccuracies about you being recorded in the study data, you have the right to request that such data be corrected. Please talk to the research team about this.

Who is organising and funding the research?

The study is co-ordinated by Vanessa Siddall and Dr Wilcock at the University of Nottingham. It is funded by The National Cancer Research Institute.

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your safety, rights, welfare and dignity. This study has been reviewed and given a favourable opinion by the Derbyshire Research Ethics Committee.

Contact for further information

Please keep this sheet to think about the study and to discuss with your family or friends. We will happily see you and your relatives or friends together to answer any questions about the study.

Whilst on the study, if you have any additional questions, please contact one of the research team on 0115 962 7619.

Vanessa Siddall	- Research Dietitian
Dr Andrew Wilcock	- Reader/Consultant
Sr Cathann Manderson	- Research Sister

Nottingham University Hospitals NHS
NHS Trust

Study Number: **07/H0401/92**

Consent Form

Title of Project: Predicting weight loss in people with cancer: Development of a screening tool.

Investigators: Dr Andrew Wilcock (Reader/Consultant in Palliative Medicine and Oncology)
and Ms Vanessa Siddall (Research Dietitian)

The patient should complete the whole of this sheet himself/herself.

Please initial each box.

1. I confirm that I have read and understood the patient information sheet version 1.3 dated February 2008 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals or the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my G.P being informed about my participation in the study. ☐

5. I agree to take part in the above study, including if required being interviewed. ☐

OR

I agree to take part in the first part of the study but do not wish to be interviewed. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of Person taking consent (If different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes.

Nottingham University Hospitals NHS
NHS Trust

Predicting Weight Loss Study

Screening for Malnutrition using the Malnutrition Universal Screening Tool (MUST)

Affix patient sticker

Date: / /

Height: metres

Weight: kilograms Body mass Index (BMI): kg/m^2

1.Body Mass Index		
BMI	MUST score	
> 20 (>30 obese)	0	
18.5 – 20	1	
<18.5	2	

2.Unplanned weight loss in past 3-6 months		
% Weight Loss	MUST score	
<5	0	
5-10	1	
>10	2	

3. Acute disease effect score	**MUST score**	
If patient is acutely ill and there has been or is likely to be no nutritional intake for> 5 days	2	

Total MUST score =

Interpretation of MUST score

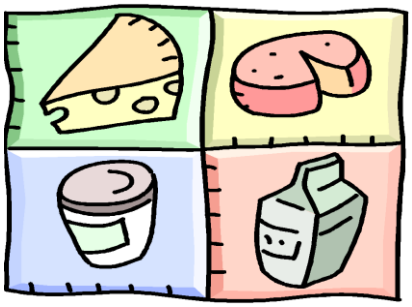
0	**1**	**2 or more**
Low Risk	**Medium Risk**	**High Risk**
Routine Clinical Care	Observe	Treat*
Repeat screening Hospital – weekly Care Homes – monthly Community – annually for special groups e.g >75 years	Document dietary intake for three days if in-patient of care in care home If improved or adequate intake – little clinical concern; if no improvement – clinical concern follow local policy Repeat screening. Hospital – weekly. Care home – at least monthly. Community – at least every 2-3 months	Refer to dietitian, Nutritional Support Team or implement local policy Improve and increase overall nutritional intake - **All patients have been given a dietary information booklet 'Getting a lot out of a little'** Monitor and review care plan Hospital – weekly Care Home – monthly Community – monthly *Unless detrimental or no benefit is expected from nutritional support

All risk categories:
Treat underlying condition and provide help and advice on food choices, eating and drinking when necessary.

Record malnutrition risk category

Obesity: Record presence of obesity. For those with underlying conditions, these are generally controlled before the treatment of obesity

GETTING A LITTLE FROM A LOT



Introduction

There may be times when you do not feel like eating very much. It is important that you eat to provide your body with enough energy, protein, vitamins and minerals. This will help with your recovery, maintain your weight and regain your strength.

If you are eating less, it is important to eat as nourishing a diet as possible.

This booklet will give you ideas for food and drinks to have when your appetite is small and suggests ways to increase the amount of nourishment in your meals.

General Hints

- Eat small, frequent meals every 2-3 hours. This is often easier than 3 main meals and can be just as nourishing.

- Drink nourishing fluids, e.g. milky drinks and fruit juice, instead of tea, coffee and water.

- Eat when you fancy and eat any time you are hungry.

- Try to avoid cooking smells if these are putting you off eating.

- Avoid drinking a lot of liquid with your meals as it may fill you up and put you off your food.

- Do not rush meals and eat slowly if you need to.

- Make the most of ‘good days’ and prepare foods which can be used when you don’t feel like cooking.

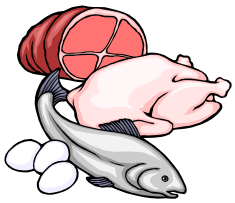
Try to include the following:-

- Use at least one pint of milk every day. Full cream milk is much higher in energy and protein than skimmed or semi-skimmed.

- You can enrich milk by adding 3 - 4 tablespoons of dried milk power into a jug of milk and stir it in well. This can be used in place of ordinary milk throughout the day.

- Dairy foods can also be good sources of protein and energy, so try to include two servings a day. This includes thick and creamy yogurts or fromage frais, 50g hard cheese or soft cheese spread, 1 bowl of milk pudding or 2 - 3 scoops of ice cream.

- Aim to have 2 servings every day of meat, fish, chicken, eggs, beans or baked beans, nuts or peanut butter as these provide protein.



- Try to drink nourishing fluids between meals. **Add hot milk** to malted drinks like Horlicks or Ovaltine, Cocoa or drinking chocolate, instant or packet soup, yeast or beef extract.

Add cold milk to blackcurrant juice, milk shake flavourings (powder or syrup), yogurt, or mashed banana or ice cream. You can use a blender to make milk shakes or try bottles or cartons of ready made milk shake

Ways to enrich your food

To make the most of your food, you should make sure that it contains lots of energy. The following foods can be useful.

- Butter and margarine. Use these generously on toast, add to vegetables and potatoes.

- Sugar, glucose syrup, treacle and honey can be added to foods to give extra energy and add sweetness but remember that they are not suitable if you have diabetes.

- Add salad cream, mayonnaise or dips to salads or sandwiches or try with breadsticks, crisps or raw vegetables as a snack.

Milk

- Use full cream or enriched milk to make up packet soups, condensed soup or soup in a cup.

- Use milk instead of water to make up jelly and instant desserts. You could also use evaporated or condensed milk.

Cream

- Add a swirl to stewed, tinned or fresh fruit or to any kind of pudding.

- Can be added into soups to give extra nourishment.

- Add into sauces, breakfast cereals or hot drinks.

Cheese

- Grate cheese and add to baked beans, eggs, soups, sauces, fish, macaroni cheese and vegetables.

- Add to jacket potatoes and mix into mashed potatoes.

- Try hard or soft cheese with crackers as a snack.

- Full fat cream cheese can be spread on bagels, scones, cake e.g. fruit, carrot or in sandwiches, bread, toast or as a dip.

Eggs

- Cook any way you wish for an alternative to meat or fish. Add cheese to egg dishes for extra nourishment.

- Egg custard can be made with enriched milk or bought, and makes a good pudding or snack.

Meat or Fish

- If meat is too tough, try a slow cooking method e.g. casseroling or use mince meat.

- Try ready minced turkey, pork or lamb for a change from beef, or use corned beef in cooking.

- Try flaking fish with parsley, cream or cheese sauce, made with enriched milk.

- Fried fish is very high in energy, if you can tolerate it.

- Tinned meat and fish can be more convenient and easier to prepare.

Soups

- Try adding minced or liquidised meat to meat soup.

- Add cheese, cream or enriched milk to creamy soups.

Yogurt and Fromage Frais

- A good source of protein. Choose thick and creamy, greek style or whole milk varieties for more energy.

- Can be used to make drinks and milkshakes.

Breakfast Cereals

- Make a good snack at any time of the day.

- Mix with full cream, enriched, condensed or evaporated milk or warm milk for a softer texture.

- Make porridge with enriched milk or add cream.

- Sweeten breakfast cereals and porridge with sugar, glucose, honey, syrup, jam (if you are not diabetic).

Nourishing Meal Ideas

- Chilled or frozen meals can be used if they are more convenient and easier for you to prepare e.g. shepherds pie, lasagne, fish pie. You could also use boil in the bag fish with a creamy sauce.

- Jacket potatoes with lots of butter and a filling of baked beans, cheese (cream or grated), fish or chicken with mayonnaise, coleslaw.

- Omelettes or scrambled eggs with added ham and/or cheese.

- Mince or stew with meat or chicken and plenty of gravy or sauce, served with potatoes boiled or mashed with butter, milk and/or cheese.

- Tinned beans, spaghetti or ravioli on bread or toast with butter and cheese topping.

- Soups with added minced meat, fish, cream or cheese.

- Macaroni or cauliflower cheese.

- Tinned or smoked fish with bread or toast and butter.

- Corned beef hash.

- Sandwiches or toasties filled with cold meat, tinned fish, hard or cream cheese, egg and mayonnaise, peanut butter. Add salad cream and mayonnaise.

- Oven ready fish or fish fingers with chips.

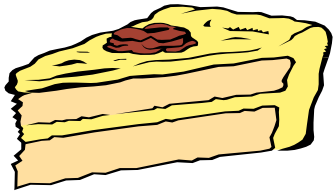
- Sausages, bacon, egg with tomato or baked beans and bread

or toast with lots of butter. Try these as a meal or at breakfast if you can manage it.

- Meat or pork pies, sausage rolls, scotch eggs with bread and butter.

Puddings and Snacks

- If you cannot face a full meal, puddings and snacks can be eaten instead and can be just as nourishing. Try eating them between meals if you cannot manage them at meal times. It can be useful to keep tins or packets in stock to eat whenever you feel you can manage.



Puddings

- Tinned rice or milky puddings.

- Tinned sponge puddings.

- Packets of blancmange, instant whip, custard or jelly, made up with enriched milk or cream.

- Trifle, cheesecake, mousse, egg custard, crème caramel can often be bought in individual portions and kept chilled in the refrigerator.

- Tinned fresh or stewed fruit, with custard or cream.

- Gateau, fruit, sponge or chocolate cake or cake slices eaten with topping of custard or cream.

- Fruit crumble or fruit pie with cream or custard.

- Yogurt, particularly thick and creamy, whole milk or greek style or fromage frais can be eaten on their own or as a topping with many of the above puddings.

- Add ice cream to any of the above puddings, or eat on its own.

Snacks

- Crackers, bread, bread rolls or toast with hard or soft cheese, pate or peanut butter.

- Toasted muffins, crumpets, pikelets, pancakes or teacakes with butter and sweet toppings.

- Nuts make a good, protein snack if you can manage them.
- Cakes, biscuits, chocolate, crisps, pastries and pies can all provide extra energy.

Food Supplements

- A range of nourishing, enriched drinks are available in a variety of sweet and savoury flavours. They should ideally be taken between meals and should not be used in place of meals. Examples include Complan, Buildup, Vita Food and Nourishment.

- Dietary supplements are also available on prescription and are sometimes recommended for certain patients.

Examples include Fortisip, Fortijuice, Enlive,Ensure, ProvideExtra, Calogen, Calshake, Maxi Jul and Polycal.

The way these are taken can vary and they are designed to suit different needs. Your doctor or dietitian will have discussed whether or not you need these supplements and if so, which type to choose and how often you should take them.

Here is an example menu to show how you could try to increase your intake:-

Breakfast:
Toast with extra butter/margarine—jam/honey/marmalade/lemon curd.
Cereal with full fat milk, extra sugar/honey.
Porridge made with enriched milk with honey/sugar.
Coffee/tea with enriched milk, sugar/honey.
Poached or scrambled eggs on toast.

Mid Morning:
Biscuits/crackers/nuts.
Milky drink made with enriched milk.

Lunch:
Meat/fish/eggs with gravy/sauce made with enriched milk/cheese added.
Mashed potatoes with extra butter/margarine/enriched
Milk added. Vegetables with butter/margarine added.

Mid Afternoon:
Milky drink made with enriched milk.
Sponge pudding/cake/tinned fruit with cream/condensed milk/ice cream.
Egg custard/rice pudding/thick & creamy yoghurt.

Evening Meal:
Soup with cream/meat/pulses added.
Toast with lots of butter/baked beans & cheese/ or jacket potato/cream cheese.

Bed Time:
Milky drink with crumpets/toast/scones & butter.

Appendix 23: G.P. letter

Please ask for: Research Team **City Hospital Campus**

Hayward House Specialist Palliative Care Cancer Unit
Hucknall Road
Nottingham
NG5 1PB
Direct Dial: 0115 9627619
Tel: 0115 969 1169 ext 46842
Fax: 0115 9627619

Title of Project: Predicting weight loss in people with cancer: Development of a screening tool

Investigators: Ms Vanessa Siddall (Research Dietitian)
Dr Andrew Wilcock (Reader/Consultant in Palliative Medicine and Oncology)

Re:

Dear Dr

I am writing to inform you that your patient has agreed to participate in a study currently being carried out at Hayward House, Nottingham City Hospital. The aim of the study is to develop a screening tool that will identify people with cancer who are at greatest risk of future weight loss. I have enclosed a copy of the patient information sheet for you to read.

If you have any questions about the study please feel free to contact me on the number above.

Yours sincerely,

Ms Vanessa Siddall
Research Dietitian

Enc: Patient information shee

Nottingham University Hospitals NHS
NHS Trust

Predicting weight loss in people with cancer: Development of a screening tool

Volunteer Information Sheet

Please read this information carefully and feel free to ask any questions or to request further information.

Investigators: Vanessa Siddall (Research Dietitian)
Dr Andrew Wilcock (Reader/Consultant in Palliative Medicine)

You are being invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. You should take time, at least 24 hours, to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

You have been invited to participate in this study as a partner or carer of someone who has cancer.

Many people with cancer will experience a reduced appetite and weight loss. This is associated with symptoms of muscle weakness, tiredness and altered mood, which can interfere with activities of daily living. These symptoms can be difficult to treat but we know that providing advice about food and diet to people as early as possible can help.

This study will ask people with cancer and their partners or carers about their experience of losing weight and any information that they have received about food and diet. From this we may be able to decide on the best way to help people with cancer maintain their weight.

Do I have to take part?

You are under no obligation at all to take part in this study. It is up to you to decide whether or not you take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form, which you will be given a copy of. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?

Along with your partner or the person that you care for, the study will involve answering questions and talking to a researcher about their appetite, weight and any advice and support that you have received regarding food and diet. You will be given the option to be interviewed at home or at the hospital. The interview should not last longer than one hour. To help us analyse the results the session will be tape recorded.

In the event of an additional hospital visit being required reasonable travel expenses will be reimbursed.

What are the side effects of taking part?

There are no side effects from taking part. For some people talking about a diagnosis of cancer and its treatment may raise emotional issues.

What are the possible disadvantages and risks of taking part?

We do not believe that there are any disadvantages of taking part other than providing approximately one hour of your time.

What are the possible benefits of taking part?

There are no direct benefits to you by taking part in this study but by taking part you are helping us to develop our knowledge of the best ways of improving services given to people with cancer.

What if something goes wrong?

If taking part in this research harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, you may have grounds for legal action but as in other cases in civil law you would need to employ a lawyer and pay for their services in the usual way. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, you may wish to contact the Trust's Patient Advice and Liaison Service

(PALS), Hospital Headquarters, Nottingham City Hospital, FREEPOST MID21426, Nottingham, NG5 1BR.

Will my taking part in this study be kept confidential?

All information that is collected about you during the study will be kept strictly confidential. The information that you provide will be entered onto a database controlled by the research team. The data will be entered onto the database in an anonymised form (e.g. you will be identified by a number not by your name). Access to the database containing the data is restricted to authorised personnel and is password protected.

What will happen to the results of the research study?

This study is being undertaken as part of a PhD educational qualification and the study results will be used to write a report as part of this qualification.

Results from the study will be published in medical journals and presented at national and international research meetings. You will not be referred to by name or be identified in any presentation or report of the study results

During this study, you have the right to access the data relating to your taking part in the study, and, in the event of any inaccuracies about you being recorded in the study data, you have the right to request that such data be corrected. Please talk to the research team about this.

Who is organising and funding the research?

The study is co-ordinated by Vanessa Siddall and Dr Wilcock at the University of Nottingham. It is funded by The National Cancer Research Institute.

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your safety, rights, welfare and dignity. This study has been reviewed and given a favourable opinion by the Derbyshire Research Ethics Committee.

Contact for further information

Please keep this sheet to think about the study and to discuss with your family or friends. We will happily see you and your relatives or friends together to answer any questions about the study.

Nottingham University Hospitals NHS
NHS Trust

Whilst on the study, if you have any additional questions, please contact one of the research team on 0115 962 7619.

Vanessa Siddall	- Research Dietitian
Dr Andrew Wilcock	- Reader/Consultant
Sr Cathann Manderson	- Research Sister

Appendix 25: Phase III volunteer consent form

Study Number: **07/H0401/92**

Consent Form

Title of Project: Predicting weight loss in people with cancer: Development of a screening tool.

Investigators: Dr Andrew Wilcock (Reader/Consultant in Palliative Medicine and Oncology) and Ms Vanessa Siddall (Research Dietitian)

The volunteer should complete the whole of this sheet himself/herself.

Please initial each box.

1. I confirm that I have read and understood the volunteer information sheet version 1.1 dated February 2008 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

3. I agree to take part in the above study. ☐

_____	_____	_____
Name of volunteer	Date	Signature
_____	_____	_____
Name of Person taking consent (If different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for volunteer; 1 for researcher.

Nottingham University Hospitals NHS
NHS Trust

Predicting Weight Loss in People with Cancer

Interview Schedule

Introduction
Explanation about proceedings
Consent

General discussion about treatment received since diagnosis
General discussion about weight history starting just before diagnosis.

1. Have you noticed any changes in your weight recently?
    a. What was the first thing that you noticed?
    b. Are there any other things that you have noticed?

2. Have you experienced any symptoms that you associate with losing weight such as: poor appetite, taste changes, feeling full quickly, sickness, bowel problems, pain, low mood, reduced energy levels.

3. What has your eating pattern been like over the last few weeks?
   24 hour recall

4. Have you received any advice about what to eat and drink either over the last few weeks or since diagnosis?
    a. What was the advice?
    b. Did you find the advice easy to follow?
        i. If not why not?
    c. When were you given the advice?
    d. Who gave the advice?

5. Is there anything that you think would have been helpful to you?

Study Protocol

Predicting weight loss in people with cancer: Development of a screening tool.

Background Information

Cachexia is a complex multifactoral syndrome the main characteristics of which are malnutrition and weight loss, anorexia and systemic inflammation. Research suggests that cachexia is the cause of at least 20% of deaths in people with cancer.[1] In addition, the prevalence of malnutrition, weight loss and anorexia in this group is up to 85% dependent on the site and stage of the disease. [2 3] Those who lose weight are affected both physically and psychologically, experiencing poorer quality of life, treatment outcomes and increased adverse symptoms.[4-7]

If treatment for cachexia and malnutrition is to be successful early detection and intervention is essential. [8] Despite the significance of nutrition in improving outcomes and maintaining the quality of life in people with cancer, this is an area in which there is little research and evidence on which to base practice. Resources available to offer nutritional support to those in need are also extremely limited.

Many nutrition related screening tools have been developed but few have been validated specifically with people who have cancer and none appear to cover the range of factors associated with cancer-related cachexia anorexia syndrome.

This study aims to assess the performance, individually and in combination of the following measures:

(i) the Appetite and Symptom Questionnaire (ASQ);
(ii) the Malnutrition Universal Screening Tool (MUST);
(iii) C-Reactive Protein (CRP) level;

in predicting percentage weight loss over three months. Taken together these three measures encompass all elements of cancer-related anorexia cachexia: appetite and symptoms affecting food intake (ASQ); weight loss and malnutrition (MUST) and systemic inflammation (CRP).

By identifying the best combination of these measures (and the exploration of the performance of shorter versions of [i] and [ii]) it is anticipated that a validated simple and practical screening tool will be developed to identify patients who are at risk of future weight loss. This will allow nutritional treatment to be prioritised and commenced where needed before the downward spiral of cachexia and malnutrition begins.

Measures

The 12 item Appetite and Symptom Questionnaire (ASQ)

The Council on Nutrition Appetite Questionnaire (CNAQ) is an established screening tool used to assess appetite. It is an eight-item tool, relating to appetite and symptoms, developed and validated within the general population in the U.S.A..[9] In 2005/2006 initial content validity testing and modification of the CNAQ for people with cancer was performed in Nottingham (Porock, Wilcock and Siddall in preparation). Using responses from service users, caregivers and health care professionals, the CNAQ has now been modified to a 12 item Appetite and Symptom Questionnaire (ASQ) which focuses on the issues specific to people with cancer and receiving cancer treatment as well as the principal symptoms affecting appetite. It is the items included in the ASQ that we will be testing and using to develop the screening tool.

The three step Malnutrition Universal Screening Tool (MUST)

NICE guidelines(2006) recommend that all patients should be screened for malnutrition using a validated tool such as the MUST.[10] The MUST, can identify those patients who have already lost a significant amount of weight but is not designed to predict future weight loss meaning nutritional treatment may be offered too late and therefore be less effective. Furthermore, previous research highlights that the MUST may not be specific enough to be used in the cancer population.[11]

C-Reactive Protein (CRP)

C-Reactive Protein (CRP) is a biochemical marker of systemic inflammation. It is an acute phase plasma protein which, during periods of systemic inflammation, as seen in the cachexia syndrome, levels

become raised. Elevated plasma concentrations of CRP (≥ 10mg/L), have been associated with adverse function and prognosis in patients with cancer.[12 13]

Overall aim of the study

To identify people with cancer who are at greatest risk of future weight loss by the development of a simple and practical screening tool.

Expected outcomes

1. An estimate of the reliability of the Appetite and Symptom Questionnaire (phase I).
2. A screening tool based on the ability of the optimal combination of items from the three measures (ASQ, MUST, CRP) to predict clinically significant weight loss over three months (phase II).
3. Estimates of the sensitivity and specificity at various cut-points of the developed screening tool in predicting clinically significant weight loss (> 10% weight loss or between 5% and 10% weight loss with a BMI <20kgm^2) over three months (phase II).
4.Exploration of the experiences of people with lung or gastrointestinal cancer and their carers regarding the initial signs of weight loss (phase III).

Methodology

There will be three phases to the study:

Phase I - Reliability study
A short-term longitudinal study, with two test-points one week apart will be used to meet expected outcome 1.

Phase II – Development of the screening tool
A longitudinal observational study with two test-points, three months apart will be used to meet outcomes 2 and 3.

Phase III - Cross examination of the screening tool
A qualitative exploratory study involving face to face semi-structured interviews.

Phase I

Patient inclusion criteria
(i)Adults, over 18 years of age, with a confirmed diagnosis of cancer, receiving radiotherapy.

Patient exclusion criteria
(i) Receiving radiotherapy to the head, neck or upper gastrointestinal tract area.
(ii) Any condition impairing their ability to swallow.
(ii) Unable to provide written informed consent and therefore complete the questionnaire due to cognitive impairment.

Patient recruitment and consent
Patients with a diagnosis of cancer (n=35) who are receiving curative radiotherapy at Nottingham City Hospital will be recruited to complete the ASQ on two occasions, one week apart. To test reliability of a nutrition screening tool subjects should have a stable weight and appetite and have minimal external factors which are likely to influence these points. The group of patients detailed above have been chosen as they:

- have a diagnosis of cancer as do the participants in Phase II of the study,
- are likely to be clinically stable over the duration of one week, i.e. not at high risk of disease or treatment related appetite and weight loss,
- are easy to access as they attend daily for treatment.

We expect to be able to recruit 35 patients within a 4 week period. Written consent will be obtained by a member of the research team at least 24 hours after the participant has been given a written information sheet about the study.

Details of power calculations and sample size
Advice has been taken from the Trent Research and Development Support Unit and by Dr Tony Arthur an expert in epidemiology and statistics at the School of Nursing, University of Nottingham.
A sample size of 35 at two time points will allow us to detect a correlation coefficient of 0.7 with 95% confidence intervals that exclude a lower limit of 0.5.[14]
This is at an appropriate level to determine the reliability of the ASQ.

Primary outcome measure
Response to the Appetite and Symptom Questionnaire

Phase II

Patient inclusion criteria
(i) Adults, over 18 years of age, with a confirmed diagnosis of primary lung or gastrointestinal cancer.

Patient exclusion criteria
(i) Lost > 10% of their pre-illness stable body weight;
(ii) Lost between 5 and 10% of their pre-illness stable body weight with a BMI < 20kg/m^2;
(iii) BMI < 18.5 kg/m^2
Those patients meeting exclusion criteria (i) – (iii) have already lost a clinically significant weight amount of weight. As we intend to develop a screening tool that will predict weight loss this group should not be included. [2 10]
(iv) Receiving enteral tube feeding or parenteral nutrition.
(v) Unable to provide written informed consent and therefore complete the questionnaire due to cognitive impairment.
(vi) Not able to be weighed.

Patient recruitment and consent
Potential participants (n=185 approx) will be those attending outpatients at Nottingham University Hospitals Trust with a diagnosis of lung or gastrointestinal cancer.
We expect to be able to recruit patients at an average rate of 15 per month from the respiratory and gastrointestinal oncology clinics at the hospital. These clinics have been chosen as patients with these cancers have a high incidence of nutritional deficiencies.[2]
Patients attending the clinic will be given in the clinic waiting area a letter from the Clinician informing them that they will be screened for risk of malnutrition using the Malnutrition Universal Screening Tool (MUST). The letter will also tell them that if their weight is stable they will be approached by a member of the research team to see if they are willing to participate in the study.
The Malnutrition Universal Screening Tool (MUST) score will be calculated and recorded by a by a member of the research team. This will involve patients having their weight and height measured and body mass index and unplanned percentage weight loss over the previous 3 to 6 months calculated. They will also be asked if due to acute illness they have had or are likely to have no nutritional intake for ≥ 5 days.
Weight and height measurements will be screened by member of research team to identify those patients who meet the study criteria.
Patients will be offered a written advice leaflet about ways to improve their nutritional intake. Those patients identified as being at risk of malnutrition from the MUST will be identified as being at risk to the Clinician in clinic by a letter in the notes.
Those patients who are **not** identified by MUST as being at risk of malnutrition, and who meet the inclusion criteria for the study will be given a patient information sheet by a member of the research team.
As long a time period that is practical within the clinic setting will be given between the patient receiving the information sheet, being approached by a member of the research team and being asked to consent. Reasoning for not giving the potential participants longer to consider taking part is that obtaining data in a timely manner is essential when investigating the prediction of weight loss over a three month period. Those patients identified at clinic as eligible to participate would be required to come back to the hospital within 2 to 3 days to be consented, complete the ASQ and have an additional blood test. This would

potentially increase levels of inconvenience and stress for the patient and be costly in terms of time and money.
Subjects will be recruited to the study over a 15 month period. Participation in the study will last for 3 months. After three months participants will have their weight measured and percentage weight loss will again be calculated. To minimise attrition, those subjects not able to attend clinic for three month follow up will be given the option to attend Hayward House at Nottingham City Hospital or to be visited at their home.
Allowing for around a 15% attrition rate we aim to end up with 160 participants.

Details of power calculations and sample size

To avoid over-fitting when building the model to develop the screening tool we will need data from a minimum of 10 participants for each item (covariate). Our target sample of 160 will allow us to include up to 16 of the items measured. [15,16]

Primary outcome measure

weight loss

At baseline participants will be weighed using calibrated scales and have their height measured by a member of the research team. They will be asked about unplanned weight loss over the previous 3 to 6 months. From this information body mass index and percentage weight loss will be calculated.
If the subject meets the inclusion criteria and consent is obtained this information will be used and they will then be asked to complete the additional outcome measures. They will be weighed at 3 months and percentage weight loss calculated over the 3 month period.

Other outcome measures

1. Malnutrition Universal Screening Tool Score

The initial screening of patients will involve all those attending clinic to have the Malnutrition Universal Screening Tool (MUST) score calculated. For those patients eligible to participate in the study the MUST score will be included as one of the outcome measures.

2. Response to the Appetite and Symptom Questionnaire

Patients will be asked to self-complete the 12 item Appetite and Symptom Questionnaire at base line.

3. Blood sampling

At baseline participants will have a venous blood sample taken to establish the level of C-Reactive Protein. Analysis will be carried out by the pathology department at Nottingham City Hospital Campus, Nottingham University Hospitals NHS Trust.

4. Clinical Condition

Diagnosis and stage of disease, treatment and performance status will be recorded at base line.

Phase III

Patient Inclusion criteria

(i) Participants of phase II
(ii) Weight loss over the three month study period.

Patient Exclusion criteria

(i) Unable to understand spoken English language.
(ii) Unable to provide written informed consent.

Volunteer Inclusion Criteria

(i) Partner or carer of a patient participant within phase II of the study.

Volunteer Exclusion Criteria

(i) Unable to understand spoken English language.
(ii) Unable to provide written informed consent.

Recruitment, sampling and consent

Potential participants will be those patients attending the out patient clinics at Nottingham City Hospital recruited into phase II of the study as described above.

At recruitment participants will be asked to indicate on the consent form if they agree to be interviewed if required.

Theoretical sampling will be adopted to ensure an appropriate selection of cases. Following the three month study period potential participants will be contacted by telephone and invited to be interviewed. Where a partner or main carer is identified by the patient they too will be asked if they are interested in participating. On agreement, a volunteer information sheet will be posted out to them and consent will be taken prior to the interview taking place. It is envisaged that including the partner or carer will add to the depth of information, particularly regarding indicators of weight loss, appetite and food preparation. The sample will also include single male and female patients.

Participants will be asked to attend Oncology Out-patients or Hayward House Palliative Care Unit at Nottingham City Hospital at a time convenient to themselves. They will also be given the option to be visited at home. As the study is exploratory it is anticipated that no more than 20 subjects will participate.

Data collection

The interviews will all follow the same semi-structured format and will be conducted in a private room with a member of the palliative care research team. Participants will be asked to recall their experiences or observations of losing weight, particularly regarding the signs and symptoms that contributed to the weight loss. Information about the amount, type and source of any dietary advice that they have received will be also be gathered as will their experiences of any influences on ability to comply. Patient participants will also be asked to complete the ASQ at this visit.

The interview will be digitally recorded and then transcribed by a member of the research team. Participants will be assigned a false name when the interview is transcribed, and the recording will be destroyed when no longer needed for study purposes.

Data Analysis

Following data cleaning procedures all data will be analysed using SPSS version 14.5 and Stata version 9. In order to increase the credibility and validity of the study, there will be triangulation of the results from all three phases.

Phase I

For test-retest reliability we will use the intraclass correlation coefficient to estimate the variation between participants in terms of ASQ scores as a proportion of the total variation. Cronbach's alpha will also be applied to test the internal consistency of the ASQ.

Phase II

To build the model that will determine the optimal set of variables that will comprise the screening tool, multiple linear regression analysis will be used. Variables will be retained where $p = <0.05$ for log-likelihood ratio tests. To address the potential problem of collinearity a correlation matrix will be used which will alert us to pairs of individual items that are highly correlated. A forward variable selection process will be used to identify the best models. This will allow greater control over the model building process and further identify any problems of collinearity.[17]

To check the robustness of the model to deviations from the model's assumptions, bootstrap resampling will be used. The optimal cut off will be determined from the ROC curve analysis which will determine the sensitivity and specificity for each cut point. Positive and negative predictive values will be estimated at each cut-off.[18]

Phase III

Data organization and retrieval will be managed using the qualitative software package NVivo. Thematic analysis will be performed on the data to highlight similarities or differences between each participant's experience with regards to a particular topic. Themes will be compared within and across all transcripts noting similarities and differences until saturation is reached. Summarisation and interpretation of the thematic analysis will permit theory development.

Dissemination

Results will be reported in peer reviewed journals such as Oncology and European Journal of Clinical Nutrition. In addition to this they will be presented at both national and international level.
At the end of the study a lay summary will be available for participants upon request

Acknowledgements

This research is funded by a project grant from the National Cancer Research Institute.

Research Activity Plan

Activity	Months							
	Jun – Aug 2007	Sept – Nov 2007	Dec – Feb 2008	Mar – May 2008	June – Aug 2008	Sept – Nov 2008	Dec – Feb 2008	Mar – Aug 2008
Ethical approval and set up								
Phase I								
Phase II Recruitment, data collection								
Phase II Follow up data collection								
Phase III data collection, transcription								
Data cleaning and analysis								
Writing publications and dissemination								

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Appendix 28: Local Research Ethics Committee study approval letter

NHS

National Research Ethics Service

Derbyshire Research Ethics Committee
3rd Floor
Laurie House
Colyear Street
Derby
DE1 1LJ

Telephone: 01332 868765
Facsimile: 01332 868785

12 July 2007

Miss Vanessa Siddall
Teacher Practitioner - Dietetics
University of Nottingham
School of Biosciences,
Sutton Bonington Campus
University of Nottingham
LE12 5RD

Dear Miss Siddall

Full title of study: **Predicting weight loss in people with cancer: Development of a screening tool.**

REC reference number: **07/H0401/92**

Thank you for your letter of 03 July 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Continued/

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application	5.3	30 May 2007
Investigator CV		30 May 2007
Protocol	1.2	July 2007
Covering Letter		30 May 2007
Summary/Synopsis: Phase I	1.2	May 2007
Summary/Synopsis: Phase II	1.2	May 2007
Questionnaire: Appetite and Symptom Questionnaire	1.1	April 2007
Letter of invitation to participant	1.2	May 2007
GP/Consultant Information Sheets	1.2	July 2007
Participant Information Sheet: Phase II	1.2	July 2007
Participant Information Sheet: Phase I	1.2	July 2007
Participant Consent Form: Phase II	1.2	July 2007
Participant Consent Form: Phase I	1.2	July 2007
Response to Request for Further Information		03 July 2007
Academic Supervisor's CV		28 March 2007
MUST Screening Tool		

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nresform.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

07/H0401/92	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Mr Peter Korczak
Chairman

Email: jenny.hancock@derwentsharedservices.nhs.uk

Enclosures: Standard approval conditions
Site approval form

Copy to: Paul Cartledge, University of Nottingham
R&D Office for Nottingham University Hospitals

Derbyshire Research Ethics Committee

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	07/H0401/92	**Issue number:**	1	**Date of issue:**	12 July 2007
Chief Investigator:	Miss Vanessa Siddall				
Full title of study:	Predicting weight loss in people with cancer: Development and validation of a screening tool.				

This study was given a favourable ethical opinion by Derbyshire Research Ethics Committee on 11 July 2007. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* (1)
Miss Vanessa Siddall	Research Dietitian	Nottingham University Hospitals NHS Trust	Derbyshire Research Ethics Committee	12/07/2007	

Approved by the Chair on behalf of the REC:

..... (Signature of ~~Chair~~/Co-ordinator)

(delete as applicable)

JENNY HANCOCK..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

Appendix 29: Research and Development study approval letter

Nottingham University Hospitals NHS Trust

Please reply to: Research and Development
E11 Curie Court
Queen's Medical Centre Campus
Derby Road
Nottingham
NG7 2UH

Telephone: 0115 970 9049
Fax: 0115 849 3295
E-mail: janet.boothroyd@nuh.nhs.uk

03 August 2007

Miss Vanessa Siddall
Nutritional Sciences
School of Biosciences, Sutton Bonington Campus
University of Nottingham
LE12 5RD

Dear Miss Siddall

ID: 07DT002 **Predicting weight loss in people with cancer: Development and validation of a screening tool.**

The R&D Department have considered the following documents:

- NHS REC Application form, version 5.3
- Protoco, version 1.2 dated 07/07
- Summary/Synopsis: Phase I version 1.2 dated 05/07
- Summary/Synopsis: Phase II version 1.2 dated 05/07
- Questionnaire: Appetite and symptom questionnaire version 1.1 dated 04/07
- Letter of invitation to participant version 1.2 05/07
- GP/consultant information sheets version 1.2 dated 07/07
- Participant Information Sheet: Phase II version 1.2 dated 07/07
- Participant Information Sheet: Phase I version 1.2 dated 07/07
- Participant Consent Form: Phase II, version 1.2 dated 07/07
- Participant Consent Form: Phase I, version 1.2 dated 07/07
- MUST Sreening Tool dated 28/03/07

Your study now has R&D approval, on the understanding and provision that you will follow the conditions set out below.

Conditions of Approval

That you:

1. Accept the responsibility of Chief/Principal Investigator as defined in the current Research Governance Framework.
2. Request written approval from the R&D department for any change to the approved protocol/study documents you wish to implement
3. Ensure all study personnel, not employed by the Queens Medical Centre, University Hospital NHS Trust Nottingham or the City Hospital NHS Trust Nottingham, hold honorary Contracts with this Trust, before they have access to any facilities, patients, staff, their data, tissue or organs.
4. Report any Serious Adverse Event involving the Trust to the R&D department, using the Trust 'policy for research safety reporting in human subjects'. Policy available from the R&D Department.
5. Complete the R&D Research Governance interim and final reports as requested.
6. Comply with the regulatory requirements and legislation relating to: Data Protection, Trust Caldicott Guidelines, Health and Safety and the use of Human Tissue for research purposes.
7. Comply with the current Research Governance Framework, available at www.doh.gov.uk or via the R&D office or Research Governance Web-site.

8. Agree to conduct this research project in accordance with ICH Good Clinical Practice and/or the MRC Guidelines for Good Clinical Practice (as appropriate)
9. Must not start your project until you have received written approval from the relevant ethics committee.

Please note that the R&D department has a database containing study related information, and personal information about individual investigators e.g. name, address, contact details etc. This information will be managed according to the principles established in the Data Protection Act.

Yours sincerely

Dr Brian Thomson / Mrs Janet Boothroyd

Director of R&D / Assistant Director of R&D

cc Nottingham Research Ethics Committee

Screening for malnutrition in cancer

Height: metres

Weight: kilograms Body mass Index (BMI): /m^2

1.Body Mass Index		
BMI	MUST score	
> 20 (>30 obese)	0	
18.5 – 20	1	
<18.5	2	

2.Unplanned weight loss in past 3-6 months		
% Weight Loss	MUST score	
<5	0	
5-10	1	
>10	2	

3. Acute disease effect score	**MUST score**	
If patient is acutely ill and there has been or is likely to be no nutritional intake for> 5 days	2	

Total MUST score: =

0	**1**	**2 or more**
Low Risk	**Risk**	**High Risk**
Monitor	Treat	Treat

Predicting weight loss in cancer

To be completed by the patient:

1. My age is…
☐ younger than 40
☐ 40 to 50
☐ 50 to 60
☐ 60 to 70
☐ older than 70

2. Most of the time my pain is…
☐ very severe
☐ severe
☐ moderate
☐ mild
☐ very mild or no pain

3. I enjoy the food I do eat…
☐ never
☐ rarely
☐ sometimes
☐ often
☐ most times

To be completed by healthcare staff:

BMI is....
☐ < 18.5
☐ 18.5 - 20
☐ 20 - 25
☐ 25 - 30
☐ > 30

MUST score is.....
☐ 6
☐ 4 or 5
☐ 2 or 3
☐ 1
☐ 0

Evaluation of Appetite and Symptoms

Please tick the box that most closely reflects your experiences with appetite and symptoms at the present time.

1. My appetite (desire to eat) is…
- ☐ very poor
- ☐ poor
- ☐ average
- ☐ good
- ☐ very good

2. Before eating, I feel hungry…
- ☐ rarely
- ☐ occasionally
- ☐ some of the time
- ☐ most of the time
- ☐ all of the time

3. When I eat I feel full…
- ☐ without having eaten anything
- ☐ after eating only a few mouthfuls
- ☐ after eating about a third of a meal
- ☐ after eating over half a meal
- ☐ after eating a full meal

4. I enjoy the food I do eat…
- ☐ never
- ☐ rarely
- ☐ sometimes
- ☐ often
- ☐ most times

5. Over the last 6 months my weight has decreased by approximately.....
- ☐ more than 2 stone (13kg)
- ☐ 1 stone to 2 stone (6kg to 13kg)
- ☐ ½ stone to 1 stone (3kg to 6kg)
- ☐ less than ½ stone (3kg)
- ☐ not at all

6. I have indigestion….....
- ☐ never
- ☐ less than once a month
- ☐ 2 to 3 times a month
- ☐ more than once a week
- ☐ all the time

7. I have a sore mouth or throat…
- ☐ all the time
- ☐ more than once a week
- ☐ 2 to 3 times a month
- ☐ less than once a month
- ☐ never

8. At present I have…
- ☐ no taste at all
- ☐ severe taste changes
- ☐ moderate taste changes
- ☐ mild taste changes
- ☐ no changes in taste

9. I feel sick or nauseated before I eat or when I eat…
- ☐ most times
- ☐ often
- ☐ sometimes
- ☐ rarely
- ☐ never

10. I vomit.....
- ☐ every day
- ☐ more than once a week
- ☐ 2 to 3 times a month
- ☐ less than once a month
- ☐ never

11. I feel constipated…....
- ☐ all the time
- ☐ every week
- ☐ 2 to 3 times a month
- ☐ less than once a month
- ☐ never

12. I have diarrhoea....
- ☐ every day
- ☐ more than once a week
- ☐ 2 to 3 times a month
- ☐ less than once a month
- ☐ never

13. Most of the time my energy level is…

- ☐ very low
- ☐ low
- ☐ moderate
- ☐ high
- ☐ very high

14. Most of the time my pain is…

- ☐ very severe
- ☐ severe
- ☐ moderate
- ☐ mild
- ☐ very mild or no pain

15. Most of the time my mood is…

- ☐ very sad
- ☐ mostly sad
- ☐ neither sad nor happy
- ☐ mostly happy
- ☐ very happy

16. I feel anxious…

- ☐ all of the time
- ☐ most of the time
- ☐ some of the time
- ☐ occasionally
- ☐ never

Other symptoms that I experience are:

_____

_____

_____