The assessment and management of unintentional weight loss associated with cachexia in a primary care setting: a mixed-methods study

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Abstract

Introduction: Unintentional weight loss (UWL) is the main symptom of cachexia, a multifactorial syndrome associated with advanced disease. Other symptoms include loss of appetite and muscle weakness. UWL in older adults can be caused by many disease processes and nutritional deficiencies. Cachexia is understudied in non-specialist care settings and primary care, as the setting for most healthcare contacts, has the potential to lead on assessing at-risk patients.

Aim: The aim of this study is to explore how unintentional weight loss in a cohort of older patients, at risk of severe frailty, is assessed and managed in primary care settings.

Research design and methods: This is a mixed-methods sequential explanatory study with four phases - systematic review and narrative synthesis; a quantitative questionnaire and case note review; qualitative semi-structured interviews with patients and caregivers; and findings across the datasets were integrated and analysed using mixed methods approaches.

Key findings: In primary care settings, weight measurements and loss of appetite were often documented in case notes, but appetite loss was normalised and rationalised by some patients. Participants expressed minimal concern about their UWL if it was sustained and more concern about muscle weakness and changes to their appearance. Living with a spouse or partner increased the likelihood of a clinical response to UWL, being overweight or obese did not. Findings suggest that lack of concern from both patient and healthcare professional perspectives impacted help-seeking behaviour and clinical responses to UWL. Especially when weight loss was not evident, was deemed to be temporary or perceived to be beneficial.

Conclusions and recommendations: Older patients at risk of severe frailty are being weighed and monitored in primary care settings. However, clinical response to UWL needs to more proactive, timely and alert to the overweight and obese patients where the impact of UWL is hidden.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACE-27	Adult Co-Morbidity Evaluation
AKPS	Australia-modified Karnofsky Performance scale
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CASCO	CAchexia SCOre
CCG	Clinical Commissioning Group
CHF	Chronic heart failure
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRP	serum C-reactive protein
CT	Computed tomography scan
DEXA	Dual X-ray absorptiometry
eFI	Electronic Frailty Index
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-CAX24	EORTC Quality of Life Questionnaire - Cancer Cachexia
EPA	Eicosapentaenoic acid
ESPEN	European Society for Clinical Nutrition and Metabolism
FAACT	Functional Assessment of Anorexia/Cachexia Therapy
HCP	Healthcare professional
ICC	Integrated Care Clinic
IPOS	Integrated Palliative Care Outcome Scale
MDT	Multidisciplinary team
MNA	Mini-Nutritional Assessment

MRI	Magnetic resonance imaging scan
MUST	Malnutrition Universal Screening Tool
NRS	Nutrition Risk Screening tool
PACE study	Proactive Anticipatory Care Evaluation study
QoL	Quality of Life
Rockwood CFS	Rockwood Clinical Frailty Scale
TNF	Tumour necrosis factor
UWL	Unintentional weight loss

List of Appendices

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Author's declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited.
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I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

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Research outputs from this thesis

Conference abstracts

- Nwulu U, Nicholson BD, Elliott-Button HL, Johnson MJ, Murtagh FE. 193 What methods are used to screen and identify cachexia and in which healthcare settings? BMJ Supportive & Palliative Care 2020;10: A77.

Poster and oral presentation

- A systematic review of the screening and identification of cachexia, by healthcare setting. (Systematic review protocol) Hull York Medical School Postgraduate Research Conference, 2018.
- The Proactive Anticipatory Care Evaluation - PhD cluster. Hull York Medical School Postgraduate Research Conference, 2020.
- What methods are used to screen and identify cachexia and in which healthcare settings? Nwulu, U., Nicholson, B.D., Elliott-Button, H.L., Johnson, M.J. and Murtagh, F.E., Palliative Care Congress, 2021

Journal article and correspondence

- Miller J, Wells L, Nwulu U, Currow D, Johnson MJ, Skipworth RJE. Validated screening tools for the assessment of Cachexia, Sarcopenia and Malnutrition: A systematic review. Am J Clin Nutr. Volume 108, Issue 6, 1 Dec 2018, 1196–1208
- Letter to the author - Christina Avgerinou, Sarcopenia: why it matters in general practice. British Journal of General Practice 2020; 70 (693): 200-201. DOI: https://doi.org/10.3399/bjgp20X709253. Nwulu U, Johnson MJ, Nicholson BD. Sarcopenia-a holistic approach is required.

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1 Introduction to cachexia

1.1 Introduction

Unintentional weight loss is a loss of weight without effort or intentionality. The causes of unintentional weight loss are numerous. Among the acute causes are sepsis, trauma, and bereavement. Weight loss could be due to inadequate dietary or nutrient intake (malnutrition or undernutrition). It could also be due to age-related muscle wasting found in sarcopenia and less commonly could be due to systemic inflammation associated with chronic or end-stage conditions (cachexia). Some of these causes are especially common in older people, which will be the focus of the thesis. But first, I will give an overview of how cachexia is defined and assessed and then provide a background to unintentional weight loss (UWL) in older adults in the following chapter.

1.2 Cachexia – development of the definition

1.2.1 Historical context of cachexia

Cachexia is a wasting syndrome long associated with terminal or advanced conditions. Cachexia marks the terminal phase of several disease processes and leads to a profound involuntary weight loss and emaciation. The word cachexia is derived from the Greek words *'kakós'* (meaning bad) and *'hexis'* (meaning appearance or condition) (1). One of the earliest mentions of a condition causing weight loss in someone with chronic disease was by Hippocrates, the noted Greek physician. Hippocrates observed an association between dropsy (oedema) and cachexia and outlined the fatal nature of the condition:

> *"The flesh is consumed and becomes water… the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest and thighs melt away…This illness is fatal."*
>
> [Hippocrates, c.460 BC- c.370 BC](2, 3)

Despite not knowing its pathophysiology, Hippocrates and fellow scholars were able to describe what they saw [muscle wasting] as a fatal progression of disease and as a marker of life-limiting illness. Since then, physicians and scientists have described wasting as part of end-stage disease. For example, without knowledge of bacteriology, the term "consumption" was used to describe a number of severe wasting conditions with tuberculosis being the most prominent cause (4). The first time that the term cachexia was linked to a specific chronic condition was in 1860 when Mauriac, a French physician, described cardiac cachexia as a: "*commonly observed secondary phenomenon in patients affected with diseases of the heart [...] a peculiar state of cachexia which is [...] conventionally designated cardiac cachexia" (1).*

By the early 1900s, the definitions of cachexia by Butler, Taylor, Barker and Osler related symptoms of cachexia (pallor, emaciation, debility, loss of strength, anaemia and anorexia) and associated it with cancer, chronic diseases and longstanding infectious illnesses (5). These definitions also attempted to explain the causes of the emaciation, with Taylor describing it as being due to *"the disturbances of the gastrointestinal tract, with the resulting loss of appetite, nausea, vomiting etc."* (6). Taylor also distinguished between two causes of cancer cachexia and that it was either due to the absorption of toxins from the tumour or the result of interference to the function of various organs (5, 6).

By the late 1900s, the medical community had begun to investigate the pathophysiology of cachexia, possible treatment options, and to clarify further the definitions of anorexia, starvation and levels of weight loss when referring to cachexia. Due to medical advances contributing to longer survival times and people living longer with chronic disease, more attention has been focused on the latter stages of chronic disease (5). Greater recognition of the need to better understand the pathophysiology of cachexia to identify possible treatment options has become evident. As the knowledge of its pathophysiology has increased, descriptions of cachexia now incorporate the contributory factors (e.g. anorexia,

early satiety, inflammation and an increased rate of metabolism); and outcomes (e.g. psychosocial distress, anaemia, treatment toxicity and death) (7).

1.2.2 Definitions of cachexia

The absence of a standardised definition and diagnostic criteria of cachexia has proved challenging to clinicians and researchers. There was a lack of agreement on a standard definition of (or diagnostic criteria for) cachexia, especially when associated with cancer.

Several definitions have been developed in the past 20 years with a concerted effort to standardise them, beginning in 2005, with the emergence of working parties, consensus and special interest groups assembled to conduct this work. Previously, cachexia and the underlying pathophysiology had been poorly understood, inadequately diagnosed and therefore rarely treated (8). Further research and the development of clinical regimens to treat cachexia was hampered because a standardised definition did not exist and diagnostic criteria were not developed (8, 9).

Baracos outlined the core components of a standardised definition in 2011. She described a *"series of core concepts"* included in the development of consensus definitions (7):

- Cachexia is characterised by depletion of body tissue (loss of weight, fat mass, or skeletal muscle mass).
- It is associated with varying degrees of reduced food intake and disordered metabolism.
- Reduced food intake is due to several disease-related and treatment-related factors, not just anorexia.
- Changes in metabolism are due to tumour growth, inflammation, increased protein and fat breakdown, and the presence of comorbid conditions.
- Cachexia progresses over time, from early and subtle changes to an advanced phase.

- There are key consequences that result from the onset of cachexia such as quality of life, physical function and increased treatment toxicity.

While these core concepts are thorough, they are reminiscent of the earlier descriptions and are related more specifically to cancer-related cachexia. A key motivation underlying the consensus work was that once a definition was agreed upon and universally used, progression into further categorising diagnostic criteria and stages would be more straightforward. The work of Fearon and Baracos in 2011 attempts to collate work conducted previously to define cachexia and represents a landmark for when the work to conceptualise standardised definitions and the diagnostic criteria for cachexia really progressed.

1.2.3 Standardised definitions of cachexia

Consensus definitions reached in the last decade include Evans' and Muscaritoli's definitions of all-cause cachexia (2008 and 2010, respectively) (8, 10) and Fearon's definition of cancer cachexia (2011) (9). Previous cachexia definitions outlined the amount of weight lost in a specific time period but did not specify the related changes in body tissue composition (11).

The first consensus definition was developed at a cachexia consensus conference in 2008 where Evans et al. proposed the following clinical definition of cachexia:

> *"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." (8)*

A special interest group, formed in 2005, within the European Society for Clinical Nutrition and Metabolism (ESPEN) considered definitions of cachexia, pre-cachexia and sarcopenia - the latter definition was developed in collaboration with the special interest group looking at nutrition in older patients. This collaboration was perceived as important as UWL occurs as a result of a number of overlapping conditions such as sarcopenia (10). Sarcopenia is defined as a loss of skeletal muscle mass and is discussed in more detail in chapter section 2.4.

Muscaritoli et al.'s definition of cachexia is a simple statement that agrees with Evans' earlier definition:

> *"...a multifactorial syndrome characterized by severe body weight, fat and muscle loss and increased protein catabolism due to underlying disease(s)." (10)*

In 2011, Fearon and colleagues used the Evans' definition as a starting point and defined cachexia due to cancer as:

> *"...a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass, with or without loss of fat mass, that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment." (9)*

The Fearon definition alludes to the many factors underlying cachexia, prioritises skeletal muscle loss and further defines cachexia as a progressive condition.
The work conducted by the three groups from 2005 and published from 2008 onwards shows how the debate around the definitions and mechanisms underlying cachexia had developed over the years. The authors started with the same concerns that a standardised definition and diagnostic criteria were required and indeed the three papers have authors in common so that attests to the continuity of this work. The main difference between the definitions is the emphasis on the loss of skeletal muscle mass (i.e., sarcopenia), to which Fearon's definition attaches more importance.

Evans' paper is a starting point and alludes to unanswered questions surrounding cachexia and encourages further discussion of (and research in) the topic area. Muscaritoli and Fearon's consensus papers build on the Evans' paper to discuss pre-cachexia, cachexia staging, the contribution of inflammation, the role of anorexia in cachexia, how to diagnose the presence of anorexia, overlapping issues with sarcopenia and cachexia as it relates to cancer.

1.2.4 Pre-cachexia and cachexia stages

While Muscaritoli and Fearon agree with the Evans et al.'s definition of cachexia, they also discuss the importance of staging cachexia, offer a definition of pre-cachexia and outline stages of progression. Cachexia, once it starts, is deemed difficult to treat with current nutritional and medical interventions so identifying markers of its development could help with early intervention.

Evans et al. in 2008, mention pre-cachexia as being related to systemic changes associated with comorbid conditions and offered a simplistic classification of cachexia staging. They suggested staging levels of mild, moderate and severe depending on the degree of weight lost in the previous 12 months (5%, 10% and 15% respectively) (8). Muscaritoli et al. define pre-cachexia as the presence of a number of the following: underlying chronic disease; weight loss of less than 5% in the previous six months; a longstanding or repeated systemic inflammatory response (indicated by inflammatory markers); and anorexia (10).

Fearon et al. also described cachexia as a continuum that moves through three stages - pre-cachexia, cachexia and refractory cachexia (9). In pre-cachexia, there are early clinical and metabolic signs such as anorexia that can precede a substantial involuntary weight loss. Progression onto the second phase of cachexia as described by Fearon depends on the cancer type and stage, response to treatment, presence of inflammation and low dietary intake.

After the publication of the consensus definitions, agreement as to the existence of a pre-cachectic phase was not universal. Some studies have developed multicomponent interventions intended to provide preventative strategies and delay further progression of cachexia (12) or to provide parallel ongoing nutritional input alongside cancer treatment regimens, again as a preventative measure (13). However, dissenting voices have not been able to identify significant numbers of patients with pre-cachexia using the above definitions in their own clinical and research settings (14).

What is not in doubt is the active phase of cachexia – termed "refractory cachexia" in the Fearon consensus definition of cancer-related cachexia (9). This stage is the result of advanced (or end-stage) cancer that is not responsive to treatment. This stage is associated with a life expectancy of less than three months and any active management of weight loss, for example parenteral nutrition, would no longer be effective or deemed appropriate (9).

1.2.5 Disease-specific definitions of cachexia

The consensus definitions of cachexia were developed in part to limit the use of a variety of definitions. However, in the wake of the consensus definition publications, disease-specific definitions have since emerged (15). Other clinical specialties are now more aware of the role that cachexia plays in chronic disease. The all-cause cachexia definition proposed by Evans et al. may be deemed inadequate. Similarly, Fearon's cancer-related cachexia may not be appropriate for other non-cancer conditions. This may have contributed to the to the emergence of disease-specific definitions. While this defeats the purpose of the consensus definitions, it is encouraging that work is being undertaken to encourage wider recognition and treatment of cachexia rather than bowing to the inevitability of its onset.

Cachexia in other chronic diseases develops differently than in cachexia associated with cancer. For instance, in cardiac-related cachexia, patients with chronic heart failure (CHF) have an earlier onset of loss of skeletal muscle mass and fewer go on

to develop cachexia (16). This contrasts with cancer-related cachexia which predominantly causes the loss of skeletal muscle after there has been a significant loss of adipose tissue (17). The priority with patients with CHF would therefore be an early loss of function due to muscle wasting and interventions which address that (such as exercise training) would be as significant as medical and dietary interventions.

Most patients with chronic kidney disease (up to 75%) receiving haemodialysis have some form of wasting/cachexia (18). A pre-cachexia condition associated with kidney disease is called protein energy wasting (PEW) and has considerable overlap with the symptoms of cachexia (19). There are issues distinguishing cachexia from other forms of wasting and malnutrition in renal patients and work is being conducted to identify a clinical phenotype for cachexia in these patients (2018) (20).

In this field, studies in cancer-related cachexia predominate and indeed the first disease-specific consensus definition that was developed was for cancer (9). The emergence of disease-specific definitions developed after the publication of the consensus definitions reflects the need to address different clinical areas. It also reflects the progression of studies and perhaps that work will be required to reach consensus in these areas in much the same way that Fearon and colleagues reached a consensus in 2011 (9).

1.2.6 Diagnostic criteria for cachexia

Of the three consensus papers outlined above, Evans and Fearon also proposed diagnostic criteria for cachexia. Evans et al.'s proposed diagnostic criteria require that UWL of at least 5% occurs in the past 12 months in the presence of an underlying disease. The weight loss must be accompanied by three of the following: decreased muscle strength, anorexia, fatigue, low fat free mass index and abnormal biochemistry (8). Abnormal biochemistry may be increased inflammatory markers (C-Reactive Protein or CRP), anaemia (haemoglobin less than 12 g/dL) or low serum albumin (less than 3.2 g/dL).

Fearon et al.'s diagnostic criteria includes weight loss of over 5% of the original body weight in the past six months (in the absence of starvation); or a Body Mass Index (BMI) of 20 or less and any degree of weight loss greater than 2% of the original body weight; or a skeletal muscle index (in the limbs) of less than 7·26 or greater than 2% (9).

There are, however, some limitations with Fearon's diagnostic criteria. A cancer patient could be diagnosed with cachexia with only one out of the three weight loss criteria. By contrast, a diagnosis of cachexia using Evans' criteria requires that weight loss in any patient with a chronic disease is accompanied by evidence of other systemic markers and loss of function, (Table 1). Further validation studies have shown that when compared, the two criteria will diagnose different proportions of the same cohort of cancer patients with cachexia. In Vanhoutte's study, 50% of cancer patients at baseline had cachexia with Fearon's criteria compared with 18% of patients using Evans' diagnostic criteria (21). By the end of the Vanhoutte validation study, 70% of the same cohort of cancer patients had developed cachexia with Fearon's criteria compared with 40% of patients using Evans' diagnostic criteria. The overall survival rates of patients with cachexia were compared to patients without it using both criteria. The difference in overall median survival rate using Evans' criteria (0.55 years with cachexia vs 1.38 years without, p=0.001) was more significant than the difference using Fearon's criteria (0.97 years with cachexia vs 1.25 years without, p=0.34). The authors felt that Fearon's criteria had less of a prognostic value and that the addition of biochemistry markers and 3 out of 4 symptoms in Evans' criteria made it a more sensitive or discriminating marker (21). The addition of sarcopenia into the statistical model did not detect a difference in survival between the patient groups (i.e., using Fearon's criteria). This study implies that the presence of weight loss alone (or even weight loss and a change in body composition) is not the determining factor of the diagnostic criteria and of overall survival. However, this was disputed by an earlier study where Martin et al. conducted a "prognostication" study in a cohort of 1471 cancer patients and found that, irrespective of BMI,

patients who presented with weight loss, low muscle index and muscle attenuation had worse survival times (8.4 months) than those with none of those features (28.4 months) (22).

Table 1: Diagnostic criteria for cachexia - Evans et al. and Fearon et al.

Fearon's criteria (cancer)	**Evans' criteria (generic)**
Weight loss >5% in past 6 months without starvation	Weight loss >5% in past 12 months and underlying chronic disease
or	OR
Weight loss >2% and BMI<20	BMI<20
or	AND 3 out of the 5 following:
	Abnormal biochemistry CRP>5 mg/L Hb<12 g/dL Albumin <3.2 g/d
	Fatigue
	Anorexia
	Decreased muscle strength
Weight loss >2% and sarcopenia	Lean tissue depletion

**Adapted from Vanhoutte, 2016*

1.3 Pathophysiology of cachexia

1.3.1 Systemic inflammation

Cachexia, it has been proposed, is due to a combination of metabolic changes and reduced dietary intake which leads to an abnormal protein and energy balance (9). Even where dietary intake remains the same, the disease process can lead to significant systematic inflammation that drives an abnormal metabolic response. Anorexia and reduced dietary intake, while, important contributory factors of the cachexic process, cannot wholly account for the catabolic weight loss experienced

by patients (17). The inability of nutritional supplementation to reverse effects of cachexia implies that systematic factors such as inflammation and catabolism may be involved (9, 23).

The body, in response to cachexia increases the breakdown of skeletal muscle tissue (known as catabolism). This is accompanied by increased resistance to the effects of insulin and an increase in lipolysis leading to reduced adipose stores (24). This differs to the body's response to starvation where lipids are used an energy source and lean body mass is preserved by a reduction in the resting energy expenditure. The cachexic response has been compared to the body's response to trauma, injury or sepsis where a sustained inflammatory response leads to a state of hypermetabolism (25). This hypermetabolic state is variously driven by abnormal tumour activity, systematic inflammation and other tumour-related and mediated effects (9).

While the pathophysiology of cachexia has been poorly defined for some years, what has emerged is a picture of systemic inflammation which is often present in cachexia patients. Inflammation is the body's response to injury or trauma and can be an acute or chronic response. In the acute phase response, the triggering factors are infection, tissue necrosis, cancer or radiation to body tissue. A number of metabolic and physiological changes are stimulated as response to the injury and the intention is to restore normal function through homeostasis and by removing the causative factor (26). The production and release of proinflammatory cytokines (e.g. tumour necrosis factor [TNF] and interleukins) mediates a systemic response which is characterised by the following features: fever, white cell breakdown, changes in lipid metabolism, increased muscle tissue breakdown, hormonal changes, increased glucose formation as well activation of the coagulation pathway (26).

TNF and interleukins induce the synthesis of C-reactive protein (CRP) which is the blood test marker for systematic inflammation and this is often present in elevated levels in cachexic patients (27). In the case of cachexia, the drive to breakdown

body tissue can be due to the underlying chronic or advanced disease state as well as the inflammatory process as cachexia can exist without overt features of inflammation (9). So, cachexia could develop in the absence of inflammatory markers such as CRP as it could be due to tumour-mediated processes or anorexic effects of the treatment rather than inflammatory causes (28).

1.3.2 Role of systemic inflammation on muscle mass

The biochemical status of hyper catabolism leads to a breakdown of skeletal muscle tissue due to increased levels of circulating hormones (e.g. cortisol, glucagon, catecholamines) and cytokines (e.g. TNF, interleukin [IL]–1β and IL-6) (29, 30). This increase in catabolic promoting molecules is accompanied by an altered response to insulin whereby insulin resistance leads to a decrease in the build-up of muscle (anabolism) and an increase in muscle wasting (30). Ordinarily, dietary proteins are broken down by the muscles into amino acids. Amino acids are direct and indirect sources of energy for the body. They are oxidised to produce carbon dioxide via the tricarboxylic acid (Krebs) cycle (indirect source of energy) and are converted to glucose and then tissue glycogen (direct source of energy) (31). In addition to this, amino acids not used at a cellular level are released into the circulation and some amino acids are converted to glucose by the liver. The levels of cellular or circulatory amino are regulated by anabolic and catabolic stimuli. Thus these stimuli regulate the rate at which protein is produced or degraded and therefore the levels of protein in the cells and how it is metabolised (30).

An increase in catabolic stimuli (or decrease in anabolic stimuli) leads to an imbalance in the way that protein is metabolised in the body. The metabolic consequences of a hypermetabolic state mean that protein synthesis, cell function and the metabolism of energy is impaired at a cellular level. Muscle mass, which is around 45% of the dry weight of an average adult human body, also has receptors for insulin, cortisol and glucagon so is important to the overall metabolism of body tissues and organs. An increase in insulin resistance inhibits the synthesis of a key enzyme that drives the glucose producing pathway in the liver. A significant

consequence of this is that the liver struggles to produce adequate levels of glucose and amino acids stored in the muscle cells are used to produce glucose thus further depleting the stores. Any derangement of the muscle cells and amino acid levels will therefore impair the glucose-dependent metabolism of cells in other body organs such as the brain and red blood cells (30).

Hypercatabolic syndrome is found in a number of acute conditions (as a response to traumatic injury, sepsis and infectious diseases) and chronic conditions (Type 2 diabetes, CHF, COPD, renal and liver failure) (25, 30). Cachexia is found to occur in the terminal stages of these chronic conditions where hypercatabolism and muscle wasting is sustained. Interestingly, hypercatabolism is also found in in older adults as part of the muscle loss encountered during the ageing process. Sarcopenia has several hypercatabolic mechanisms in common with cachexia due to the loss of protein reserves that drives the muscle wasting. However, this muscle wasting in sarcopenia can be due to a combination of non-disease factors such as immobility, poor dietary habits and poor dietary intake (32, 33).

1.3.3 Adipose tissue lipolysis

Derangement to the metabolic system in the body (hypermetabolism) that leads to proteolysis also drives the increased breakdown of adipose tissue (lipolysis) and a reduction in the formation of fat tissue (lipogenesis). Adipose tissue lipolysis is regulated by several neural and hormonal factors that become affected by conditions such as obesity, and cachexia. Lipolysis-regulating hormones are stimulatory (catecholamines and natriuretic peptides) and inhibitory (insulin) and their separate mechanisms of action converge at a final-rate limiting stage of lipolysis activation (34). Lipolysis results in the release of fatty acids that are used as energy substrates and they also signalling molecules and substrates for lipoprotein production in the liver (34). Therefore, states of hypermetabolism will affect the tight regulation of lipolysis and lipogenesis. Dysregulation is thought to be due to the insulin resistance that is present as a result of metabolic imbalances (35). There is emerging evidence that while hypercatabolism and hypermetabolism leads to loss of skeletal muscle mass, in cancer-related cachexia lipolysis is

activated by the effects of tumour-activity and this occurs before skeletal muscle loss (17). Tumour-derived factors such as "tumourkines" (cytokine IL-6 and parathyroid hormone related protein) lead to lipolysis and thermogenesis which in turn leads to a reduced adipocyte size and loss of visceral fat (36).

Body composition studies of cancer patients who have lost weight demonstrated that the weight loss was mainly due to adipose tissue loss with marginal losses in skeletal muscle mass (17). This loss of adipose tissue before skeletal muscle mass may also be partly due to the levels of obesity in the general population. It has been proposed that the extent of cachexia in a patient can be underestimated and missed in the early stages if the patient is obese (37). It has also been proposed that cytokines, as inflammatory mediators, are associated factors that will trigger loss of adipose tissue before skeletal muscle (36). Furthermore, the presence of obesity-related insulin resistance suggests that there are already metabolic disturbances in the body before the tumour-derived factors activate lipolysis.

1.3.4 Role of insulin-resistance in cachexia

Insulin plays a significant role in the balance of amino acids in the body. After a meal is consumed, there is an increase the blood glucose levels which triggers a release of insulin from the pancreas. Insulin decreases blood glucose levels by reducing hepatic glucose production and increases glucose uptake in muscle and fat tissue (38). As an anabolic hormone, insulin stimulates lipogenesis and inhibits lipolysis and increases protein synthesis and inhibits protein breakdown. By comparison, lipolysis is promoted by catabolic agents in the form of catecholamines, cortisol and glucagon (38).

Originally insulin-resistance was described as resulting from the wasting process that occurs during cachexia (39). However, increasing importance has been placed on the role of insulin in the maintenance of skeletal muscle and that a decrease in its action is a contributory factor in the wasting process (39).

1.4 Epidemiology of cachexia

Cachexia develops in many disease states, such as cancer, chronic illnesses (organ failure, chronic obstructive pulmonary disease [COPD] and rheumatoid arthritis) as well as in chronic infections (e.g. human immunodeficiency virus [HIV]) (40). Published studies have estimated cachexia as being prevalent in 5–15% of patients with heart failure, 30–60% of patients with chronic kidney disease (CKD), 27–35% of patients with COPD and 50–80% of patients with cancer (41-43). When examining the population prevalence of cachexia, the most frequent cachexia subtypes (in order) are: COPD cachexia, cardiac cachexia, cancer cachexia and CKD cachexia (44).

Cachexia prevalence in cancer patients varies widely with studies estimating that it occurs in 50–80% of cancer patients (41-43). This variation is due to the site of the cancer, the stage of cancer and differing clinical definitions being used to diagnose the cachexia between studies (41, 43). Cachexia prevalence is highest in lung (60%) and in pancreatic and gastrointestinal cancers (up to 80%) (41). Fifty percent of patients with lung cancer have cachexia at the time of diagnosis and 75% will go on to develop it during their treatment (45). The most dramatic variation in prevalence in one study compared three cachexia definitions (Fearon [2006], Evans [2008] and Fearon [2011]) in a cohort of 405 cancer patients and found that the prevalence varied from 12% to 85% (46). Prevalence is a theme in the systematic literature review conducted in the first phase of this PhD study and is described in greater detail in Chapter 4.

The global prevalence of cachexia has been estimated as 9 million of the world's population and in 1% of the population in western countries (44). These figures have been estimated using the prevalence of the underlying conditions and applying data from cachexia studies. These prevalence figures are also reliant on accurate data being collected and the most accurate statistics are from the West and from Japan (47). Despite the limited data on cachexia in African countries, the role of cachexia in causing deaths is likely to be higher and more impactful than in the West due to the lack of access to treatments for the underlying causes such as

chronic infections (e.g. HIV/AIDS) and cancer (47). What should also be considered is the rise in the levels of chronic diseases in lower and middle-income countries which will lead to an increased prevalence of cachexia associated with those conditions. Therefore, one would expect the prevalence of cardiac cachexia, for example, to increase.

Mortality rates of patients with cachexia varies with estimates of 15–25% of such patients dying with COPD per year; 20–40% of deaths per year of CHF and CKD patients with cachexia; and up to 80% of patients dying per year with some advanced cancers (pancreatic or non-small cell lung cancer) (48). von Haehling estimates that in industrialised countries, 1.5 million–2.0 million deaths occur in patients with cachexia a year (2016). Estimations from an earlier von Haehling study, attributed 20% of deaths from cancer as being directly due to the effects of cachexia (44).

1.5 Assessment and diagnosis of cachexia

Cachexia is under diagnosed and poorly managed in the average hospital setting (49, 50). It may be diagnosed by using combinations of anthropometric measures (usually body weight and BMI), biochemical tests (such as albumin and CRP), measuring body composition (total body water and fat free mass) and using nutritional screening tools (12, 51).

Additionally, but not commonly used in clinical practice, muscle strength as a measure of function can be estimated by measuring hand grip strength which is an indicator of the muscle strength in the upper extremities (52). However, one of the earliest indicators of the onset of cachectic syndrome is loss of appetite (anorexia) and asking about weight loss in the intervening 6 months should be a relatively simpler place to commence assessing for cachexia. Other assessment methods will be outlined in this section and will also be described in the systematic review which is reported in Chapter 4.

1.5.1 Nutritional screening tools

In assessing anorexia and food intake, eliciting details as to the patient's current dietary intake compared to their normal diet is a standard first line assessment (9). This assessment is a common tool for identifying weight loss, malnutrition, dietary intake and risks of developing nutritional problems as a result of the above. Furthermore, it gives health care professionals an opportunity to address the causes of the weight loss, loss of appetite and or a limited dietary intake where possible. There could be mechanical, treatment or disease-related causes that lead to the loss of appetite or inability to eat normally (9).

Nutritional screening tools have been used in clinical practice due to a lack of similar screening tools to specifically identify cachexia. In addition to various factors, screening tools assess nutritional status, loss of appetite and unintentional weight loss, so they can be useful for screening and assessing any UWL that is related to cachexia.

The ESPEN endorses the use of the Malnutrition Universal Screening Tool (MUST) for use in the community (53, 54); Nutrition Risk Screening tool, the NRS- 2002, for use in hospital settings (54, 55); and the Mini-Nutritional Assessment (MNA) is the tool recommended for used in older populations (56), Table 2. These recommended screening tools do not all address cachexia-specific factors such as muscle mass and function, metabolic and inflammatory disorders and quality of life issues. The screening tool, of the three, that most addresses cachexic features is the MNA. The MNA has screening questions that covers mobility, psychological distress and neuropsychological problems. However, the screening scores will only categorise the patient as having a normal nutritional status, being at risk of malnutrition or being malnourished. As the focus of all these assessments are only relevant for one aspect of the cachexic condition, they appear to have limited utility for recognising those patients at risk of developing or who have cachexia. This has been addressed by the development of cachexia-specific screening tools (57, 58).

1.5.2 Cachexia specific screening tools

While nutritional screening tools can address various features relevant to cachexia such as a low BMI, weight loss and loss of appetite, only one validated screening tool has been developed for specifically to screen for cachexia - The CAchexia SCOre (CASCO). CASCO is a score incorporating five different factors related to cachexia: body weight and lean body mass loss; anorexia; inflammatory, immunological, and metabolic disturbances; physical performance; and quality of life (57). This score attempts to classify the degree of cachexia through a scoring system with four cachexia stages: mild (less than 25 on the scale); moderate (more than 26 and less than 50); severe (more than 51 and less than 75); and terminal (more than 76 and up to 100) (57). Additionally, the CASCO score is weighted to reflect the importance in which the authors/developers place in the five different factors. Body weight and composition accounts for 40% of the score; inflammatory, immunological, and metabolic disturbances accounts for 20%; physical performance and anorexia account for 15% of the score each; and quality of life accounts for 10% of the score.

While CASCO is the only validated cachexia-specific score there are some limitations. It has been validated designed for use in hospital settings (59) as it was developed for staging the cachexia present in cancer patients. To what extent is can then be used for other chronic conditions is currently unclear. Also, most assessments, with exception of the anorexia and QoL questionnaires, require physical and clinical measurements such as dual X-ray absorptiometry (DEXA), blood tests and physical functioning measurements such as grip force, climbing stairs or a 6-minute walk distance test. The authors intended that CASCO would be used as soon as possible after the cancer diagnosis (57) and this presumes it being used in a secondary care setting as part of specialist cancer treatment. They did, however, validate a mini-CASCO score at the same time which reduces the number of laboratory parameters and has a physical functioning questionnaire (ibid). The mini-CASCO score correlated strongly with the full CASCO score and so could be a less resource intensive tool although a DEXA scan or conventional

bioelectrical impedance analysis (BIA) is still required to measure the lean body mass (59).

Table 2: Comparison of nutritional screening tools recommended by ESPEN

Name	**Population**	**Nutritional screening parameters**	**Reliability**	**Validity**
Malnutrition Universal Screening Tool (MUST) (53)	Adults – acute and community	BMI Weight loss (%) Acute disease effect score	*Quoted to be internally consistent and reliable. Very good to excellent reproducibility Kappa = 0.8 – 1.0*	*Face validity, content validity, concurrent validity with other screening tools (MST and NRS) Predicts mortality risk & increased length of stay and discharge destination in acute patients*
Nutrition Risk Screening tool (NRS-2002)(55)	Acute adult	Recent weight loss (%) Recent poor intake (%) BMI Severity of disease Elderly	*Good agreement between a Nurse, Dietitian and Physician Kappa = 0.67*	*Retrospective and prospective analysis. Tool predicts higher likelihood of positive outcome from nutrition support and reduced length of stay among patients selected at risk by the screening tool & provided nutrition support*
Mini-Nutritional Assessment (MNA)(60)	Community, sub-acute or residential aged care settings	Screening and Assessment component Includes diet history, anthropometry (weight history, height, MAC, CC), medical and functional status. Numerical score: - no nutritional risk - at risk of malnutrition or	*The reliability (inter-observer variation) was estimated, Kappa =0.51 (61)*	*Content validity index (M-CVIA-C) was calculated by averaging indicator scores weighted per domain, quantifying to what extent the methods covered the construct of malnutrition. Acceptable content validity was defined as M-CVIA-C ≥0.80. MNA has a content validity*

		- malnourished		*index score (M-CVIA-C) = 0.75(62)*

*Adapted from (63) / ESPEN - European Society for Clinical Nutrition and Metabolism / MAC – mid-upper arm circumference / CC – calf circumference

1.5.3 Anthropometric measures

Diagnostic methods for cachexia include the assessment of body anthropometry using either body mass index (BMI) or estimated weight loss (recalled by the patient or carer), or by directly assessing body mass composition using DEXA, BIA, computed tomography (CT) or magnetic resonance imaging (MRI) scans.

The most common assessments are that of weight – usually as BMI (body weight in kg divided by height in metres squared) and of weight loss – as a percentage of weight lost in a time period. Consensus definitions of cachexia incorporate a BMI of below 20 kg/m^2 and a weight loss of 2% or 5% of the original body weight lost in the previous 6 or 12 months (8, 9). A BMI of 20 kg/m^2 is classed as normal but a BMI of 18.5 kg/m^2 and below is classed as underweight (64).

While CT and MRI scans are the most accurate methods of measuring body composition, they are radiographic modalities that can be impractical and expensive (65) although cancer patients will have repeated scans as part of their treatment. By contrast, BIA as an indirect method of assessing body composition is more widely available and is non-invasive and inexpensive (ibid). BIA involves a measuring scale with footpads that allow a harmless electrical current to be sent through the body. The rate at which the current goes through the body and the levels of resistance or "impedance" it meets (water vs fat tissue) allows for an

estimation of the water in the body and by calculation the fat-free mass and body fat levels. BIA is however less accurate in patients with significant electrolyte or fluid imbalances or abnormalities (66) so may not work for patients with advanced cancers or chronic kidney disease.

When assessing body mass composition, the following measures are commonly used:

1. Fat mass (FM),
2. Lean body mass (LBM),
3. Lean body mass index (LBMI-calculated by dividing LBM by the square of the patient's height)
4. Appendicular skeletal muscle (ASM)
5. Appendicular skeletal muscle index (ASMI – calculated by dividing ASM by the square of the patient's height). ASMI is used to determine the presence of sarcopenia (67, 68).

1.5.4 Biochemical tests

Biochemical laboratory tests can also be used to demonstrate the underlying metabolic and inflammatory markers that may accompany cachexia.

Markers demonstrating an abnormal biochemistry can be investigated through a full blood count. Patients could be anaemic (haemoglobin less than 12 g/dL) or have a low serum albumin (less than 3.2 g/dL). One accepted index of systemic inflammation is serum C-reactive protein (CRP), although cachexia is not always accompanied by signs of inflammation (9).

1.5.5 Muscle strength and other measures of function

Measuring handgrip strength is a non-invasive easy to conduct a test that is regarded as a surrogate for upper body strength (69, 70). This is usually assessed through the use of a dynamometer on the patient's dominant hand. It can be used to assess change of strength over time and can predict mortality (69, 71). Other measures of function include assessing the patient's physical performance through

recording their levels of total activity, assessing their ability to climb stairs and recording their 6-minute walk distance (57).

1.5.6 Quality of life measures

In research settings, psychosocial status has been measured using quality of life (QoL) questionnaires, either generic health related QoL measures, cancer related QoL measures or one of the few cachexia-specific QoL instruments such as Functional Assessment of Anorexia/Cachexia Therapy or FAACT (72) and a more recently developed EORTC QLQ-CAX24 measure for cancer patients with cachexia (73).

1.5.7 Management of cachexia

The management of cachexia depends on the underlying cause, prognosis and other patient-related factors. Potential treatments may include appetite stimulants, anti-inflammatory drugs, exercise training and anabolic agents, in combination with nutritional supplements and anti-catabolic interventions, although the evidence is conflicting as to the benefits and safety of these treatments(41, 74-76). A more detailed description of treatments for cachexia is beyond the scope of this thesis, which focuses on identification and assessment. However, an overview of some of the treatments that have been reported in the literature is reported in Table 3.

Table 3: Cachexia treatments and interventions

Type of treatment	**Name**	**Mechanism of action**
Pharmacologic interventions	Megestrol acetate Medroxyprogesterone Acetate Dronabinol Ghrelin Anamorelin Prednisone	Appetite stimulant
Pharmacologic interventions	Cyproheptadine Thalidomide Pentoxifylline Eicosapentaenoic acid (EPA)	Cytokine inhibitor
Pharmacologic interventions	Nandrolone Decanoate Oxandrolone Corticosteroids	Anabolic agent
Pharmacologic interventions	Celecoxib	Non-steroidal anti-inflammatory drug (NSAID)
Supplements	Vitamins Amino acids – glutamine, carnitine, Adenosine Fish oil - Omega-3 fatty acids and EPA Medium chain triglycerides	Various
Nutritional	Dietary advice and counselling Liquid nutritional supplementation	
Physical activity	Exercise and resistance treatment	

1.6 Summary

This chapter summarises the evolving knowledge of cachexia as a potentially treatable condition rather than just a marker of deteriorating disease. A significant component of this evolution is the development of a standardised definition and a diagnostic framework of cachexia through consensus work with experts in the field. What remains clear is that the knowledge of the pathophysiology of cachexia is still evolving and therefore effective treatment options for cachexia, once established, remain elusive. The key symptom and core component of the definitions and diagnostic frameworks is UWL. The following chapter will outline the main causes of UWL and how it may be encountered in primary care settings, with particular reference to an older patient population with chronic conditions and end-stage disease.

2 Unintentional weight loss in primary care settings

2.1 Introduction

Within the United Kingdom (UK), primary care is the first level of care accessed for non-emergency conditions and minor injuries and 90% of all health care contacts occur in primary care settings (77). In the case of clinical care for those with chronic conditions, general practitioners (GPs) are responsible for everyday care and are the gatekeepers and referees for specialist care. This chapter will give an overview of the impact of the changing demographics of the UK population on primary care service utilisation and some context to the mixed picture the GP needs to contend with when managing unintentional weight loss (UWL) in a comorbid population. There is an increase in comorbidity with increasing age and the study population, that I chose to study for the prevalence and experiences of UWL, was aged 65 and above and at risk of moderate to severe frailty.

2.2 Changing demographics and the impact to primary care

The rise in the older aged adult population in many countries is a testament to the improvements in public health (improved housing, sanitation and food safety) and in health care (vaccinations, antibiotics, advances in critical care and surgical techniques). This has led to patients surviving infections and trauma that were previously fatal and living longer with chronic conditions (78). In 2016, 18% of the UK population were aged 65 and over; estimates predict that this will increase to 25% by 2046 (79). Long term-conditions are more prevalent in older people and 6 in 10 adults in the 2001 UK household survey reported having some form of a chronic health condition, such as a mental health issue, strokes, cancer and Type 2 diabetes (78).

In some cases, cancer can now be classed as a chronic health problem. Cancer becomes more common with age and 66% of people living with a cancer diagnosis are over the age of 65 (80). Additionally, the number of people with cancer is

increasing by 3% every year and by 2040, it is estimated that 25% of the population over 65 will be cancer survivors (80). Survival rates have improved as a result of advances in cancer screening, detection and treatment. This can be demonstrated by the cancer registry figures in England and Wales over a 40-year period. In 1971, the one-year net survival after diagnosis was 50% but by 2011, 50% of patients are still alive *10 years* after diagnosis (81). Consequently, depending on the cancer type, patients can survive cancer and die from other long-term conditions. Additionally, an increasing number of patients can survive recurrences of their cancer with some of their symptoms being managed as a long-term condition.

The increase in an older comorbid population has challenged health service resources as people with chronic conditions access healthcare more often than those without chronic conditions. People with chronic conditions account for 80% of primary care consultations and have 9 consultations a year compared with the average of 4 consultations per patient per year (82). Patients with multimorbidity are also up to 7 times more likely to be admitted to hospital (78) and once there risk having longer hospital stays (83). When symptoms of these chronic (and advanced) conditions are reviewed, anorexia and weight loss are commonly experienced and UWL can lead to loss of function and increase the rate of decline in these patients (84, 85).

2.3 Causes of UWL in older comorbid populations

The main component of cachexia is UWL which is primarily due to loss of skeletal muscle mass. Weight loss in older adults is common with getting older due to natural changes in body composition. However, about 15-20% of older people experience weight loss of either 5 kg or 5% of usual body weight (86, 87). While some of the weight loss can be due to temporary or irreversible causes, Table 4, other causes can be due to age-related changes in body composition or due to underlying organic disease with associated increased mortality (88-90).

Early recognition and investigation of UWL provides an opportunity for intervention and early diagnosis of a number of conditions (91), Table 4. UWL is commonly encountered in healthcare settings and the cause of the weight loss can sometimes be problematic to diagnose when there may be multiple causative factors. Investigations can further be complicated in older patients in whom UWL is more common and may be age-related as well as due to their comorbidities. In the next section, I will outline two of the most common causes of UWL in older people.

Table 4: Causes of unintentional weight loss in older age adults

	Causes of weight loss
Cardiopulmonary diseases	Congestive heart disease, chronic lung disease, lung cancer
Connective tissue disease	Rheumatoid arthritis
Endocrine disorders	Type 2 diabetes, hyperthyroidism
Gastrointestinal disorders	Ulcers, carcinomas, malabsorption syndromes, inflammatory bowel disease, strictures, achalasia
Haematologic disease	Lymphoma
Infectious diseases	Tuberculosis, endocarditis
Nutritional disorders	Malnutrition
Psychiatric diseases	Depression, anxiety, schizophrenia, dementia
Psychosocial causes	Poverty, social isolation, access to food, cognitive impairment
Renal disease	Chronic kidney disease
Other causes	Medications, dental and oral health problems, alcoholism, oropharyngeal carcinomas, advanced metastatic cancers, unknown/idiopathic

Adapted from Alibhai 2005 (92)

2.4 Significant causes of unintentional weight loss

2.4.1 Malnutrition

A well-accepted definition of malnutrition is "a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" (93, 94). Malnutrition as a clinical term can refer to 'undernutrition' where there is insufficient dietary intake with a resulting loss of fat and muscle mass; or 'overnutrition' where excessive dietary intake leads to increased fat mass and or nutritional deficits (95). The challenge in identifying and treating malnutrition has been the lack of a standardised or generally-accepted diagnostic criteria (96). In addition, a confusing number of terms have been used interchangeably with malnutrition such as undernutrition, depletion, wasting and protein-energy malnutrition (94). In this thesis, the term malnutrition is classified as 'undernutrition' where used.

In older patients, malnutrition which leads to a loss in muscle mass has been associated with a decrease in muscle strength and impaired physical function (97). In terms of general medicine hospital admissions, moderate or severe malnutrition is associated with more severe disease, a longer hospital admission and worse patient health outcomes (98). A number of multi-centre studies have estimated that 23-60% of older patients in acute hospital settings are malnourished and that 22-28% are at risk of malnutrition (99). Considering that older patients, 65 years and older, comprise 50% of adult hospital inpatients in the NHS (100), there is significant cost to the healthcare system when malnutrition is not addressed.

The European Society of Clinical Nutrition and Metabolism (ESPEN) proposed that malnutrition should be diagnosed when a patient has either a low BMI (<18.5 kg/m^2), or UWL in addition to either a reduced BMI (<20 kg/m^2 for <70 years or <22 kg/m^2 for ≥70 years) or a low fat free muscle index (FFMI) using sex-specific cut-offs (94). The levels of UWL were described as greater than 10% over an indefinite time period, or over 5% weight lost in the last 3 months (96). In addition to diagnosis, malnutrition risk should be determined in at risk populations. As

malnutrition risk is high in older patients and often underrecognized, recommendations have been made to screen for it early on in healthcare interactions (101). Screening for malnutrition can lessen or prevent deterioration of physical function, improve healing and recovery, and reduce the length of hospital stay (101).

The many terms for malnutrition and its multiple causative factors (physiological, social and economic) have led to the development of a number of screening tools using a range of parameters (102), see also Table 2:

- The Nutritional Risk Index (NRI) (103) and the Geriatric Nutritional Risk Index (GNRI) (104) - both use biochemical and clinical indicators.

- The Mini Nutritional Assessment Screening Form (MNA-SF) (105) and the Malnutrition Universal Screening Tool (MUST) (54) - both use anthropometry, mobility, cognitive state, self-perceived health and nutrition indicators (102).

- The Malnutrition Screening Tool (MST) is a two-question screening tool which uses the presence of UWL and poor dietary intake as indicators of malnutrition risk (106).

- The Nutrition Risk Screening 2002 (NRS-2002) tool uses medical history in addition to clinical and subjective judgement (107).

As can be seen above, malnutrition as the cause of UWL is relatively common in an older patient population. Identifying the cause of UWL can be complex as it can be caused by the combination of malnutrition, sarcopenia (see below) and cachexia in at-risk older patients. The use of nutritional screening tools is becoming mandatory in some healthcare settings (especially acute hospital care) and while this is beneficial to care there is a danger in ignoring other causative factors of the UWL (99). It can be argued, however, that screening for malnutrition risk and

treating it where it is identified is a priority. The major factor that distinguishes malnutrition from other causes of UWL is that it can be reversed when adequate dietary intake is achieved (99, 108).

2.4.2 Sarcopenia

There is an age-related change in body composition, a decline in muscle mass, from the age of 40 onwards (109). It can be challenging to estimate the prevalence of sarcopenia due to the various methods used to assess muscle mass and the heterogeneity of study populations (110). Von Haehling and colleagues report estimates of sarcopenia prevalence of 5–13% of people aged 60–70 years and that prevalence rises to 11-50% for those aged 80 or above (110). Sarcopenia is a major cause of falls, increased risk of fractures and functional deterioration in the older population (111). Furthermore, sarcopenia can lead to difficulty in performing activities of daily living, loss of independence due to mobility issues and an increased risk of death (110-112).

Awareness in the research and clinical communities that a decline in lean muscle mass was associated with a decline in strength and loss of function led to consensus work on how to define and diagnose this decline as a condition (112). The condition was named 'sarcopenia' in 1989 by Rosenburg and the word is derived from the Greek words *'sarx' (*flesh) and *'penia*' (loss) (112). Evans and Campbell were the first to describe sarcopenia in 1993 as *"[…]the age-related loss in skeletal muscle mass, which results in decreased strength and aerobic capacity and thus functional capacity"* (113), however the first consensus definitions were not developed until the next decade.

The International Working Group on Sarcopenia arrived at a consensus definition in 2009:

> *"Sarcopenia is defined as the age-associated loss of skeletal muscle mass and function. The causes of sarcopenia are multifactorial and can include disuse, altered endocrine function, chronic diseases, inflammation, insulin resistance, and*

> *nutritional deficiencies. Although cachexia may be a component of sarcopenia, the 2 conditions are not the same. The diagnosis of sarcopenia should be considered in all older patients who present with observed declines in physical function, strength, or overall health. Sarcopenia should specifically be considered in patients who are bedridden, cannot independently rise from a chair, or who have a measured gait speed less than 1 m·s^{-1}." (114)*

In addition to the consensus definition of sarcopenia, sarcopenia should also be considered in patients with the following:

- difficulties in performing activities of daily living,
- a history of recurrent falls,
- documented recent weight loss,
- a recent hospitalisation,
- or have chronic conditions associated with muscle loss (e.g. Type II diabetes, chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA) and chronic kidney disease (CKD) and malignancies).(114)

The European Working Group on Sarcopenia in Older People further categorised sarcopenia as primary sarcopenia where there is a progressive loss of muscle mass and function due to ageing (where there is no other cause) or secondary sarcopenia due to other causes such as lack of activity, disease-related or nutrition (109). The European Working Group also arguably developed a more clinically useful working definition of sarcopenia in 2009 with recommended assessment tools for use in clinical practice and research (115). The working definition and recommendations were updated in 2019 to reflect the research and clinical advances made in the interim (109). The 2019 operational definition uses low muscle strength as the primary parameter of sarcopenia as the working group perceived that muscle strength was the most reliable measure of muscle function:

> *"[…] sarcopenia is probable when low muscle strength is detected. A sarcopenia diagnosis is confirmed by the presence of low muscle quantity or quality. When low muscle strength, low muscle quantity/quality and low physical performance are all detected, sarcopenia is considered severe."* (109)

The assessment tools recommended by the European Working Group are mostly found in clinical settings and they proposed that physical performance be measured to assess the severity of sarcopenia (109). Muscle strength, they suggested, could be assessed using hand grip strength and the chair stand test (chair rise test) (109). Skeletal muscle mass may be measured by dual-energy X-ray absorptiometry (DEXA) scans and bioelectrical impedance analysis (BIA) with magnetic resonance imaging (MRI) scans an option for research settings. Additionally, physical performance can be evaluated using gait speed or a timed-up-and-go test amongst other assessments techniques (109).

2.5 Frailty in primary care settings

The British Geriatric Society defines frailty as a *"distinctive health state associated with ageing where the multiple body systems lose their in-built reserve*" (116). It has been estimated that 10% of people aged 65 and over have frailty, rising to about 50% prevalence in the over 85 (117). Frailty predisposes an individual to disability by making them more to physical and physiological stressors and is therefore associated with increased risk of adverse outcomes such as falls, hospitalization, and death (118, 119). Frailty also be characterised by symptoms such as UWL, fatigue and weakness, chronic breathlessness and low physical activity (117, 119). Fried and colleagues identified a frailty phenotype that was predictive of falling incidents, worsening mobility or difficulty with activities of daily living, hospitalisation, and death (119). Identifying and assessing frailty early on, therefore, will reduce the development of the previously mentioned symptoms, adverse outcomes and disability.

The prevalence of frailty increases in later life, but exact rates differ between studies. Reported prevalence rates vary from 3 – 37%, in people aged 65 and over, due to the use of different frailty scores and a lack of consensus as to a universal definition (120). Two approaches to define frailty in an operational manner, are the use of the frailty phenotype or the use of a frailty index. The frailty phenotype defines frailty as a syndrome that is due to decline across multiple physiological states (119). This approach views frailty as existing when 3 or more of five physical features are present: UWL, weakness (e.g. low hand grip-strength), exhaustion, slow walking speed and low physical activity (119, 121).

Frailty indices can be used to quantify frailty by counting the number of accumulated risks for each patient. Frailty indices do not just focus on the nature of deficits but the amount and therefore the cumulative risk of the deficits (122). The areas of deficit are not limited to physical signs, by contrast to the frailty phenotype, but they cut across many domains.

Frailty screening tools that have been developed and utilised in clinical settings include the following (122):

- Clinical Frailty Scale (or Rockwood CFS) which is an assessment tool based on a clinical evaluation in the domains of mobility, energy, physical activity, and function, see below (123).
- Groningen Frailty Indicator is an assessment tool that considers 15 deficits in four domains - physical, polypharmacy, cognition, and psychosocial (124).
- Tilburg Frailty Indicator uses an assessment of 15 deficits in physical, psychological, and social domains (125).
- The Edmonton Frail Scale includes 17 deficits in multiple domains - cognition, overall health, social support, medication, nutrition, mood, continence, and functional performance (126).

- The FRAIL scale is a five-item scale that considers deficits accumulated in domains that form its acronym - Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight (127).

A widely used frailty screening tool is the Rockwood Clinical Frailty Scale (CFS) developed in 2005 as part of the Canadian Study of Health and Aging (123). This scale was originally a 7-point scale but is now a 9-point measure of frailty that can be used to summarise the overall level of physical functioning or frailty of an older adult after a clinical encounter (128). The scale uses descriptions of frailty levels to stratify older adults according to their levels of vulnerability. The scale ranges from a level of 1 (very fit) to 9 (terminally ill) with a life expectancy of less than 6 months.

Screening tools can identify the risk of poorer outcomes and increased mortality in older patients with complex care needs. Increased frailty in older patients leads to increased risk of hospitalisation or 'unplanned hospital admissions' (129). This has resource implications and the assessment of frailty is therefore important for planning care and policy development (130). The use of a frailty screening tool has been recommended in guidelines for best practice in the care for older patients (123). Most screening tools have been developed for use during a clinical admission or encounter. There are tools that have been developed to calculate frailty risk automatically from patient records. This proactive risk assessment process is especially important in primary care settings where most healthcare contacts take place.

Clegg et al. developed an electronic Frailty Index (eFI) which was an electronic algorithm that was validated for use in primary care settings to define and categorise frailty risk (131). The eFI uses a 'cumulative deficit' model, which measures frailty based on the accumulation of a range of deficits - which can be symptoms, clinical signs, diseases, disabilities and abnormal test values (131). Once the eFI algorithm is incorporated into an electronic health record system, it uses

Read codes (a coding system) to identify up to 36 deficits. It then calculates a score which falls into one of the following frailty risk categories (131):

- Fit (eFI score 0 - 0.12) – People who have no or few usually well controlled long-term conditions. This group generally live independently.
- Mild frailty (eFI score 0.13 – 0.24) – Where slowing down in older age leads to some help needed with personal activities of daily living (e.g. finances, shopping, transportation).
- Moderate Frailty (eFI score 0.25 - 0.36) – People with difficulties with outdoor activities and possible mobility problems or who require help with activities such as washing and dressing.
- Severe Frailty (eFI score > 0.36 = 13 or more deficits) – Dependence on personal carers and may have a range of long-term conditions/multimorbidity. Some in this group may be medically stable but others may be unstable and at risk of dying within 6 to 12 months.

Management of frailty in older people is complex and the use of a multidisciplinary assessment approach is recommended to identify and quantify frailty in individual patients. This enables clinicians to focus clinical interventions and refer for onward psychosocial interventions where needed. In NHS England, GPs are contracted to use an 'appropriate screening tool' to identify all patients aged 65 and above who may be living with moderate to severe frailty (132). For those with severe frailty, around 3% of the over 65s (131), GPs need to undertake an annual medicines review and a falls assessment if clinically appropriate. GPs are encouraged to consider an annual medicines review and a falls assessment in patients with moderate frailty (~12% of the over 65s) (131, 132).

The ideal clinical environment to assess older patients for frailty would be an integrated patient-centred service delivered in a setting with links to primary, secondary and community care systems. A Comprehensive Geriatric Assessment (CGA) is a holistic review of a patient which allows for care planning. CGA is considered the gold standard for the management of frailty in older people (116). It

is a process of care that involves a multidimensional assessment of a patient by a number of multidisciplinary specialists in older people's health.

The domains which are reviewed in a Comprehensive Geriatric Assessment include (116):

- Physical symptoms and underlying illnesses and diseases.
- Mental health symptoms (including memory) and underlying illnesses and diseases.
- Level of function in daily activity, both for personal care and for everyday life functions.
- Social support currently available, both informal (family, friends and neighbours) and formal support (social services carers, meals, day care).
- Living environment – state of housing, facilities and comfort. Assessment of ability and tendency to use technology and local transport.

The CGA appointment usually take 90 minutes or more and can involve – a GP or care of the elderly physician, a pharmacist, a social worker, and a physiotherapist or an occupational therapist. The end product of a CGA is typically an individualised care and support plan that is tailored to the patient's needs, wants and priorities (116). The CGA is seen as beneficial to both the health care system for care planning and reducing unwanted admissions as well as a beneficial to the older patient and their care givers. As part of the CGA, patients and their care givers should be given information and resources about how and when to seek further intervention. It enables them to be more proactive in some aspects of their care and it also provides an opportunity to discuss preferences and possible options for end-of-life-care (116).

2.6 Sarcopenia, frailty, malnutrition and overlap with cachexia

In Evans' consensus definition of cachexia, a distinction was drawn between cachexia and weight loss associated with other factors; such as loss of muscle mass

(sarcopenia), conditions that effect dietary intake, and other causes of malnutrition (8). This distinction was necessary due to the underlying mechanisms that drive the weight loss and the association with chronic or advanced disease states. Sarcopenia has been termed a 'multi-faceted geriatric syndrome' (115). Indeed, in older people, it may be difficult to pinpoint only one cause of sarcopenia due to a multiplicity of factors such as comorbidities, physical inactivity and loss of appetite leading to changes in eating habits. Disease-related sarcopenia is associated with advanced conditions and can therefore be confused with cachexia as they can have many overlapping symptoms. Of relevance to this thesis, is that in an older population, cachexia is always associated with an advanced disease state whereas sarcopenia related to ageing can occur in an otherwise healthy ageing population and can be halted or reversed (8, 10).

As outlined in the previous section, frailty is a complex condition that has several contributory factors. The frailty phenotype as described by Fried et al. has similar components to cachexia of UWL, exhaustion, impaired physical activity and physical function and muscular weakness (119). A number of the frailty screening tools, previously described, have UWL and loss of appetite as a 'deficit' or domain that contributes to frailty risk. The Groningen Frailty Indicator has a 'Nutrition' question: *Has the patient unintentionally lost a lot of weight in the past 6 months (6 kg in 6 months or 3 kg in 3 months)?* (124). The Tilburg Frailty Indicator has a 'Physical Component' question: *Have you lost a lot of weight recently without wishing to do so? ('a lot' is: 6 kg or more during the last six months, or 3 kg or more during the last month)* (125). The Edmonton Frail Scale has a 'Nutrition' question: *Have you recently lost weight such as your clothing has become looser?* (126). And the FRAIL scale has 'Loss of weight' as one of its domains where loss of weight is scored 1 for respondents with a weight loss ≥ 5% within the past 12 months based on self-report (127). The eFI also has 'weight and anorexia' as one of the 36 deficits that are used to calculate the frailty risk (131).

Both cachexia and sarcopenia can be associated with frailty (108, 133) and the loss of physical function experienced in people with frailty can impact physiologic

mechanisms such as inflammation, insulin-resistance and changes to coagulation (119, 134, 135). An increase in an older population living longer with chronic conditions has led to the emergence of complications made more severe and or protracted by the presence of frailty or sarcopenia (136, 137). It is postulated that sarcopenia and frailty have systematic inflammation as a common mechanism of action, amongst other mechanisms (134, 136, 138). It is therefore possible, that in an older patient with a chronic disease any UWL could be due to cachexia, age- or disease-related sarcopenia or frailty or any combination of the three.

Malnutrition and cachexia are two different entities with a superficially similar presentation when malnutrition is severe. However, malnutrition equally affects the loss of muscle as well as fat mass and can be reversed with nutritional support (139). Where the four 'tissue loss syndromes' of sarcopenia, frailty, cachexia and malnutrition have been examined simultaneously in a patient group – a complex picture emerges (140). In a group of older medical hospital patients (≥70 years), sarcopenia was the most prevalent condition (42%), frailty and cachexia were prevalent in 33% and 32% respectively and malnutrition was the least prevalent in 15% of the patients (140). Two-thirds of the patients had at least one of the syndromes with considerable overlap and 8% of the inpatients had all four of the syndromes (140).

2.7 Interventions for cachexia, unintentional weight loss and sarcopenia

As previously described in Chapter 1, potential interventions for cachexia may include appetite stimulants, anti-inflammatory drugs, exercise training and anabolic agents, in combination with nutritional supplements and anti-catabolic interventions (41, 74-76). Cachexia, once established, is very challenging to reverse and treating the underlying cause (i.e. cancer) can often ameliorate its impact. However, there is limited evidence on the use of dietary counselling, with or without oral nutritional supplements and at the current time, no pharmacological intervention has been recommended as the standard of care for cancer-related cachexia (141).

Unintentional weight loss has many contributory factors and is a symptom that both sarcopenia and cachexia have in common. UWL needs to be investigated to understand the underlying mechanisms and causative factors. As can be seen in the previous section, however, a number of conditions overlap and can be present in the same patient, especially in the older patient with frailty (142).

Both sarcopenia and cachexia as conditions or syndromes have different aetiologies so require different therapeutic approaches or interventions once identified. There are inconsistent views as to how both conditions can be identified and managed - even by dietitians (143). Treatment strategies for both cachexia and sarcopenia have been focused on improving energy and protein intake, which is known to be mostly ineffective for treating cachexia (144). Currently treatment options for sarcopenia involve targeting the loss of muscle mass and nutritional deficiencies (145) and include - resistance exercise, protein supplementation, and vitamin D. Nutritional supplements and physical activity have been used to prevent or reverse muscle mass depletion in older patients with age-onset sarcopenia (146).

2.8 Rationale for this study

Cachexia, and its impact, is understudied in primary care and community settings. The literature and evidence base concerning cachexia has predominantly investigated its physiopathology and evaluated possible interventions. Therapeutic interventions have mainly been evaluated in secondary care settings and predominantly in cancer-related causes of cachexia (147). This is to be expected as the specialised care for patients with chronic and end-stage conditions will be in secondary care settings. However, much of the care closer to the patient's residence is located in primary care and is undertaken by a workforce who may act as the patient's care coordinator and may have greater knowledge of the patient's life, other comorbidities, and family and domiciliary arrangements.

The management of cachexia in patients with advanced disease presents a resource challenge for the health care system that is set to rise as the population ages and people live longer with cancer, organ failure and other chronic conditions. Cachexia increases the risk of frailty and the likelihood of adverse outcomes especially in the last year of life (117, 119). Clinicians now, more than ever, need to factor in the impact of frailty and any UWL as indicators of functional decline and poor prognosis when treating patients with chronic conditions (136, 137, 148, 149).

While it is known that cachexia as experienced by patients, is a distressing part of their condition, it is a natural part of the trajectory to death especially in patients with cancer (150-152). Interventions for cachexia delivered once the cachexia symptoms are well established often have a limited expectation of success. The pathophysiological mechanisms driving catabolism are often too entrenched and prove to be irreversible. One objective of Fearon and colleagues, in staging the cachexic process, was to see if there could be opportunities to intervene at an earlier stage (9). It could be argued that primary care has an important part to play in the early intervention of this complex syndrome as primary care health professionals would be able to either pick up unintentional or unexplained weight loss.

Finally, the lack of standardised definitions and diagnostic criteria for cachexia have hampered the identification and management of cachexia by healthcare professionals in all healthcare settings. There are opportunities for primary care services, as the setting for most health care contacts, to lead on assessing patients who may have conditions which make them at risk for developing cachexia. A number of assessment tools have been developed for the identification of frailty and malnutrition in comorbid older patients. The next potential step in this cohort could be assessing them for cachexia or the risk of developing cachexia, amongst other underlying causes, when they begin to experience loss of appetite and UWL especially in primary and community care settings.

2.9 Summary

This chapter defines cachexia as a complex multifactorial condition associated with several disease processes and caused by a combination of pathophysiological mechanisms. The main symptom of cachexia is UWL, and this can be present in other syndromes such as malnutrition, sarcopenia and frailty – especially in an older patient population with chronic and advanced diseases. There is increased use of screening tools for malnutrition and frailty in primary care settings. As cachexia has a pre-cachexia phase, there may be an opportunity to also identify patients at risk from developing refractory cachexia. The impact of cachexia and overlapping causes of UWL to primary care have been described to set some context to this thesis.

Chapter Three will describe the methodology, study design and methods used in this PhD study.

Chapter 4 will then provide further context in the form of a systematic literature review to describe the methods used to screen and identify cachexia and which health care settings cachexia studies are conducted.

3 Research design and methodology

3.1 Introduction to research aims, methodology, study design and methods

This thesis set out to describe the identification and assessment of cachexia symptoms as when patients present in primary care settings. Due to the study settings and informed by the literature review, the study concentrated on the main cachexia symptom of unintentional weight loss (UWL).

Mixed methods were deemed appropriate for exploring the phenomenon of UWL in patients at risk of developing cachexia. Quantitative methods were used to describe the patient cohort, to measure how much weight they had lost, and how it was assessed and documented in primary care records. Qualitative interviews were used to explore how UWL was experienced by patients and family caregivers and how it was perceived, recognised and managed in primary care settings.

This PhD project is comprised of an overarching aim and five objective which I will now outline before describing the research questions, the study design and the study setting. There are four study phases that I will describe and will outline the research methods, data collection and data analysis for each phase.

3.2 Research study aim and objectives

The aim of this PhD project was to explore how UWL, as the main symptom of cachexia, is identified and assessed in patients with chronic and malignant conditions in primary care settings.

The overarching aim raised the following objectives:

1. To identify and describe the tools and methods used to screen for and assess the symptoms of cachexia, and in which health settings as presented in the published literature.

2. To determine the prevalence of UWL and loss of appetite in the last 12 months in older patients at risk of UWL. These symptoms were used as a proxy for cachexia risk.
3. Within a cohort of older patients, at risk of moderate to severe frailty, to describe the characteristics of those with UWL in the 12 months and to compare their demographics, comorbid conditions, and functional status to those without UWL.
4. To describe if and how primary healthcare professionals document weight measurements and the assessment of UWL in the clinical record.
5. To elicit the views of those with UWL (and their caregivers) about their symptoms; their experienced of how their symptoms have been assessed and managed by healthcare professionals in primary care settings; and what advice or guidance they were given about this weight loss.

3.3 Research questions

This PhD project (and its components) addressed the following research questions using mixed methods and were conceptualized into four inter-linking phases, see Table 5. An important aspect of mixed methods research is that there is the potential to integrate at one or a number of study stages and that the different approaches used inform and draw on each other. I will now define the research paradigm of mixed methods, the rationale for using this approach and how the studies were integrated.

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Table 5: Four-phase mixed methods study design

	Research questions	**Study design/method**
Phase 1	Literature review 1. What tools or methods are used to identify and assess cachexia symptoms and in which healthcare settings?	Systematic review of the literature
Phase 2	***The nature of self-reported unintentional weight loss*** 2. What proportion of the patients have self-reported UWL during the previous 12 months before attending an integrated care clinic? 3. What are the characteristics of patients with self-reported UWL in the previous 12 months compared with those without? ***The nature of documented unintentional weight loss*** 4. What proportion of the patients have documented UWL during the previous 12 months before attending an integrated care clinic? 5. What are the characteristics of patients with documented UWL in the previous 12 months compared with those without? 6. What factors are associated with a with documented UWL in the previous 12 months? ***Self-reported unintentional weight loss and associations with documented unintentional weight loss***	Cross-sectional survey and case note review

	7. When patients report UWL in the previous 12 months, how many have unintentionally lost weight as recorded in their primary care records? 8. What factors are associated with a self-report of UWL in the previous 12 months? ***Weight loss measurements and management of unintentional weight loss as recorded in primary care records in a 12-month period*** 9. How often are older patients, who have been assessed for frailty, weighed in primary and community care settings as documented by health care professionals in a 12-month period before attending an integrated care clinic? 10. In what kinds of primary and community healthcare appointments are weight measurements of these older patients, routinely collected? 11. What assessments are used (or referrals made) for weight loss in these patients? 12. What proportion of these patients are further investigated for the cause of their weight loss in the 12-months before attending an integrated care clinic? 13. What are the characteristics of patients who have a management action* for their UWL in the previous 12 months compared with those without? 14. What factors are associated with the management* of UWL, as documented in the primary care records of older patients, in the 12 months before attending an integrated care clinic for frailty management?	

	(*assessment / investigation / referral / treatment)	
Phase 3	**Qualitative study** 15. What are the experiences of patients (and caregivers) with UWL of their symptoms and of the assessment and management of their symptoms in primary care?	Semi-structured interviews with patients and family caregivers.
Phase 4	**Mixed methods integration/data analysis** 16. How is UWL assessed and managed in primary care and experienced by older patients who might be at risk of developing cachexia?	Integration and analysis of research findings from the quantitative and qualitative phases.

** A 'management action' was a composite measure that reflected the presence of one or more of the following in the case notes during the previous 12 months: an assessment of appetite or nutrition, an investigation ordered in primary care (blood test, scan or x-ray), a referral to other healthcare service for further investigation or treatment, or a treatment to address the weight loss (e.g. dietary supplementation).*

3.4 Study design – mixed methods

3.4.1 Definition and rationale

Qualitative research methodologies are used to explore the nature of a phenomenon and describe an individual's experience, while quantitative methodologies measure the strength of an effect, assess causality and the generalisability of results (153). Although there is no universal definition of mixed methods research, Creswell and Plano Clark (2011) outline its core characteristics: in a single research study, both qualitative and quantitative strands of data are collected and analysed separately and integrated—either concurrently or sequentially – to address the research question (154). Mixed methods research, therefore, utilises the strengths of both qualitative and quantitative research methods to understand a research problem from different perspectives (155). It is suitable for answering multifaceted research questions found in applied health research or health services research due to the complex, multi-layered systems and processes often encountered in healthcare (153).

Mixed methods are used in a number of scenarios and have several rationales for why they should be used rather than an individual research method. Greene et al. identified five main purposes for using mixed methods:

- Triangulation: combining research methods to counteract the inherent biases of each and correlating/validating the results of each method. This strengthens the credibility of the findings.
- Complementarity: Incorporating both approaches enhances the significance of the results and balances the weaknesses of one approach with the strengths of the other. So, one method is used to elaborate, enhance, clarify and illustrate the results of the other method.
- Development: using the results of one method to inform or develop any or all stages of the other method.
- Initiation: used to amplify the findings from one research method by analysing them through the perspective of another method or paradigm to gain new perspectives, contradictions and definitions.

- Expansion: used to broaden the breadth and range of research findings by using different methods for various research components (156).

A systematic review of published mixed methods research found that while one-quarter of the 232 social sciences studies reviewed did not reveal a rationale for using mixed methods, the most common reasons outlined were complementarity (28.9%) and expansion (25.4%), with triangulation (7.8%) and initiation (0.4%) being rarely used (157).

3.4.2 The philosophical background of mixed methods research

Research paradigms are defined as a shared perspective or worldview about how the world works or *"universally recognized scientific achievements that for a time provide model problems and solutions to a community of practitioners"* (158). A paradigm is intended as a set of common practices, assumptions and beliefs that evolve into a set of norms or frameworks associated with a field of study (158-160). Each research paradigm is based on a different set of assumptions about what reality is (ontology) and the nature of knowledge (epistemology), which is reflected in the methodological approaches used to generate knowledge, and the research methods are the tools used to answer research questions (161).

Quantitative research is based on the scientific paradigm of positivism, which in the scientific tradition involves the collection of verifiable data or empirical observation (162). The ontological position of positivism is realism, and the epistemological position is of objectivism. The positivist stance holds that there is only one version of the truth (one reality) that can be measured using robust and valid tools (163). Knowledge is acquired and tested, while the researcher remains objective by being independent of what is being researched (164). The single existing reality is not situated in a political or historical context (161). The associated methods for generating quantitative data tend to be experimental or correlational studies that examine causality (161). These studies can involve the testing of hypotheses and causal relationships between variables, which can lead to the prediction or generalisation of findings. Existing theories are used to test

these relationships and hypotheses (deduction). Post-positivism, a more moderate version of positivism, has since emerged, with critical realism as its ontological position. Post-positivism still adheres to examining causal relationships, reductionism, empirical observation and theory verification. However, it acknowledges that complete objectivity is unobtainable due to the social conditioning of the researcher; therefore, there is a degree of uncertainty in how knowledge is gained and interpreted (165).

The most dominant underlying paradigms for qualitative research are the interpretive/constructivist paradigms (166). In these paradigms, there is no single reality but rather multiple realities based on one's interpretation or construction of reality (163). In contrast to the positivist paradigm, the methodology associated with interpretivism seeks to understand the phenomenon from an individual's perspective and investigates interactions among individuals and the historical and cultural contexts in which people inhabit (166). The researcher (their philosophical stance, experiences and beliefs) can also influence how knowledge is interpreted. Interpretive methods such as interviews, focus groups and open-ended questionnaires are used to examine behaviour and explain actions from the perspective of the participants (165). These methods generate qualitative data, which are analysed based on the researcher's interpretations, and the interaction between researcher and participant plays a role in this interpretation. By induction, qualitative data are used to build theory from the 'ground up' (112). Furthermore, qualitative data produced by these methods are highly contextualised and therefore have limited transferability, unlike quantitative data.

Mixed methods research (MMR) has been referred to as the 'third methodological movement' and proposed as a new research paradigm. In one form or another, mixed methods have been used as a research methodology for more than 50 years and are increasingly employed in the health sciences and other interdisciplinary fields (167). However, Creswell and Pano Clark identified the origins of mixed methods or 'MMR proper' as an intentionally used methodology in a single study in the late 1980s (168). The establishment of MMR as a separate and distinct

methodology has been evident in the emergence of standard texts (165, 167) the Journal of Mixed Methods Research, established in 2007, and a research association – the Mixed Methods International Research Association, founded in 2013 (167).

The rise of MMR as a distinct methodology has resulted in academic clashes as to how the opposing paradigms of positivism (or post-positivism) and constructionism can be used in a single study due to their perceived incompatibility (Howe 1988, as cited by Johnson and Onwuegbuzie (169)). These 'paradigm wars' were between qualitative and quantitative purists who contended that the differences between the two orientations were too big to overcome and that it was impossible to accommodate between them (169). The differences in approaches and epistemology were seen as the main issue rather than the practicality of combining the different research methods. This was disputed by mixed methods researchers, and certainly the evidence of the many studies conducted using this methodology and the 'institutionalisation' or wider adoption of mixed methods research has since contradicted these disputes (167).

3.4.3 Pragmatism and mixed methods research

The ontological and epistemological standpoints of a researcher significantly impact the study design and objectives, as well as, consequently, the types of knowledge they generate. These paradigmatic stances differ from researcher to researcher, but these differences are sometimes viewed as artificial (170). Despite their paradigmatic stances, it has been suggested that health researchers are becoming more pragmatic in their research methods (170). This pragmatic approach may be reflected in the increased use of mixed (integrated components) or multiple (separate components) research methods in the same research study (168).

Pragmatism, as a research paradigm or worldview, is commonly aligned with the use of mixed methods research, as it allows the use of multiple methodologies (167). A pragmatic approach places value on both subjective and objective knowledge and advocates use approaches based on 'what works' (168). Emphasis is

placed on the research questions, guiding the choice of the quantitative and qualitative data collection methods used to answer them. This allows the researcher to tailor their approach to better answer their research questions (169).

The ontological stance of pragmatism is that there are multiple perspectives of reality. Reality is not fixed; it is renegotiated, debated and interpreted in order to flexibly handle different research stances and methodologies (171). This is especially useful for examining a phenomenon from different angles and perspectives. The epistemological stance is one of 'practicality', as the methods used are those best suited to answer each research question, and the methodologies used are quantitative and qualitative, resulting in a 'plurality of methods' (169).

3.4.4 Research design overview: a sequential explanatory study

There are several approaches to conducting mixed methods research, including triangulation, embedded, explanatory and exploratory designs (168). Each design has a distinct purpose; an emphasis on the sequence/timing of the component research methods (concurrent vs sequential) and specified time points when the approaches are integrated (167).

In this PhD study, I have used a sequential explanatory study design (see Figure 1). The sequential explanatory study design has two phases: the first phase involves collecting and analysing quantitative data, and the second employs qualitative methods to elaborate on the first phase's results. There is a data connection (or integration) between the quantitative and qualitative phases. The integration of data facilitates the analysis or interpretation of the findings from both phases. There are two variations in the sequential explanatory study design. In the participant selection model, quantitative data are used to identify participants for a more detailed qualitative study. In the follow-up explanation model, qualitative methods are used to elaborate on and explain any differences or statistical associations found during the quantitative phase (154). When the participant

selection model is used, the qualitative phase of the study becomes the more dominant of the two phases.

In this thesis, I have used mixed methods (Figure 1) to examine the phenomenon of UWL from the perspectives of patients and caregivers (through the use of qualitative interviews) and from the perspective of healthcare professionals (recorded in case notes and retrieved through case note reviews). As this particular research topic, related to a primary care context, has few relevant studies in this setting, my own study is, therefore, more descriptive. Employing mixed methods indicates that the researcher is looking to take advantage of the strengths aligned to each methodology and to pragmatically choose the most suitable methodological approach for each research question. I made use of the 'complementarity' rationale as outlined by Greene et al. where using both approaches offset the limitations of each approach (156). In using case note review as part of the quantitative phase, my work was limited by what was documented in the electronic health records. The qualitative interviews allowed me to elaborate on or clarify the results of the quantitative phase.

The participation selection model of the sequential explanatory study design was used in this study. The quantitative phase of the study, therefore, had two purposes – to study the characteristics and demographics of all recruited participants and to identify a sample of suitable participants (who had experienced UWL in the past 12 months) for the qualitative phase. The qualitative phase of this study was the most dominant of the phases, and it described the experiences of patients and family caregivers. Additionally, data integration in this study design occurred at three time points: the use of the quantitative findings to guide the qualitative sampling, cross-referencing some of the quantitative findings with the qualitative interviews, and at data analysis – where findings from both phases were integrated. In Figure 1, the notation of 'quan' and 'QUAL' (in uppercase letters) are used to denote the dominance given to each phase and the sequence of the phases (quan before QUAL) (172).

3.4.5 Study design limitations and advantages

The main advantage of mixed methods research is that the shortcomings of either quantitative or qualitative research as a single method can be offset by the strengths of the other. For example, qualitative data (quotes, narratives) can be added to quantitative data (descriptive or analytical statistics) to add meaning or insight. This approach, when conducted purposively, can provide a deeper understanding of a phenomenon by examining the findings of the mixed method, where they meet or agree with each other (169).

Other strengths of mixed methods research include the flexibility with which data can be described and reported; it enables the researcher to explore unexpected results generated from collated data; and it can be used to assist in the development of an instrument or framework to direct the research. Importantly, it gives a voice to study participants and ensures that study findings are grounded in participants' experiences (173-176).

The disadvantages of using mixed methods research are that the act of integrating quantitative and qualitative components increases the complexity of the research process. This leads to a more time-consuming process that may require additional collaborative work in research teams with members with the expertise required to conduct the research. Additionally, it may be difficult to identify points of integration in the quantitative and qualitative components; for sequential studies, it might be challenging to delineate when each phase should commence. Furthermore, during the analysis, there may be challenges in resolving discrepancies between the different types of data.

In this PhD project, the sequential study design allowed the introduction and exploration of early themes that emerged during the quantitative phase. Limitations of the mixed methods approach are that the points of data integration, as outlined below in Figure 1, have been decided *a priori*, but the researcher cannot determine whether the results can be truly integrated until the study is completed. For instance, the findings of one phase may not be reflected in another phase and strategies would be needed to analyse discrepant or contradictory findings. This

will be explored further in Chapters 7 (Phase Four: Integrated Findings) and Chapter 8 (Discussion and Conclusions).

Mixed methods research needs to be carefully planned to outline all aspects of the research. This includes how to recruit study samples for both components, how to time each component, and where to integrate while maintaining methodological rigour and quality for each component.

QUAL: qualitative; *quan:* quantitative; + - concurrent; → - sequential.

uppercase letters: high priority or dominant phase; and *lowercase letters*: low priority or non-

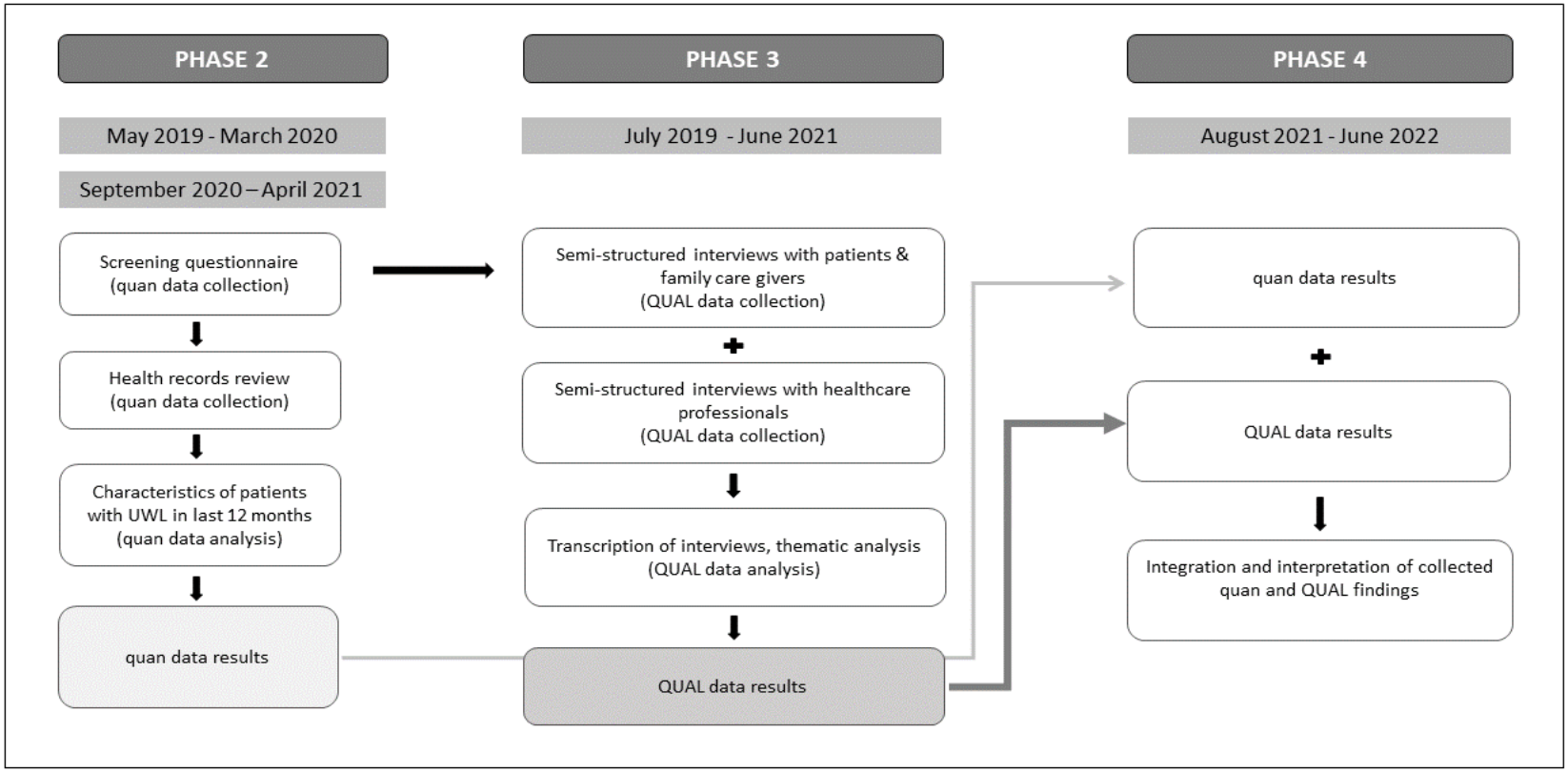


Figure 1: The integration of mixed methods approaches in study phases 2-4

3.5 Study setting

3.5.1 Recruitment from the Integrated Care Clinic and care homes in Hull

The study setting for this PhD study was conducted at an integrated care clinic and four care homes in the Hull region. The Jean Bishop's centre in East Hull was opened in May 2018 and housed an integrated care clinic (ICC) that provided proactive anticipatory care to people in the Hull region who had been identified by their GP practice as having severe frailty. The majority of GP practices in the Hull CCG region were invited to screen their patients' lists for those with severe frailty, as identified by an electronic Frailty Index (eFI) score of 0.36 or above. The eFI is a score based on the accumulation of several deficits from 36, which are comprised of Read codes, as described in section 2.5. The score is predictive of adverse outcomes, and if a patient over 65 has 13 or more deficits (≥ 0.36), they are more likely to be admitted to a care home (HR of 4.76, 95% CI 3.92–5.77), hospitalised (HR of 4.73, 95% CI 4.43–5.06) and die within a year (HR 4.52, 95% CI 4.16–4.91) than those of the same age who are fit or have mild or moderate frailty (131).

Once identified, patients with severe frailty were invited to attend the ICC at the Jean Bishops Centre. After a pre-assessment visit to the patient's home, this appointment was arranged with the patient to assess their current health concerns and needs. The patients were informed what to expect during their appointments with a clinician (either a specialist in geriatric medicine or a general practitioner with a special interest), a pharmacist, a physiotherapist and an occupational therapist. There was also a social worker and a representative from Carers UK to talk to patients and their family caregivers as needed. The clinic ran from 08:30 to 13:00, and patients were evaluated by the members of the multidisciplinary team (MDT), as listed above. This was classed as the 'patient journey'. Those who required transportation to and from the clinic received it, and the appointment concluded with a free meal in the clinic's café. The MDT team also offered a similar assessment to care home inhabitants in the Hull region on a rota basis. Recruitment of a small subset of participants occurred at four care homes, as the MDT assessment was rolled out across the Hull region.

3.6 Evaluation of the ICC – the PACE study

The Proactive Anticipatory Care Evaluation (PACE) study commenced at the end of May 2019. The main study was a service evaluation of the ICC in the form of a non-randomised matched control trial with three PhD sub-studies using mixed method approaches. The research team recruited 300 participants who had been assessed by the ICC (250 from the Jean Bishops Centre and 50 from care homes) and controls who were yet to be assessed or were not residents in the Hull region. The research team consisted of three PhD students (Helen Elliott-Button, Sophie Pask and me) and one post-doctoral research associate (Dr Mabel Okoeki). There was additional input from Alex Bullock (AB), a research dietitian undertaking a clinical doctoral fellowship.

The main aim of the study was to assess the impact of the MDT assessment on the short- to medium-term health and wellbeing of patients compared with controls. A baseline questionnaire with screening questions was administered to study participants at the time of the assessment… Participants also gave consent for the research team to access their health records to get demographic details, details of comorbidities, medications and intervention details from the MDT team at the ICC.

The PhD students were not involved in recruiting controls, and only used baseline data collected from participants who had received the intervention. Each student had a different focus for their PhD, and they used the PACE data and related sections of the baseline questionnaire to identify participants for the qualitative component of their mixed methods PhD projects. This PhD project was therefore, one of three sub-studies linked with the PACE service evaluation.

3.7 PACE study team contributions

Although the participants were recruited by a researchers' team, the following phases of this PhD project were either designed or conducted entirely by me, with minor exceptions:

1. The systematic review of the literature focused on a topic specific to my sub-study. I conducted the searches, data extraction and narrative review with the assistance of one of the PACE study researchers (HE-B), who served as my second reviewer.
2. I helped design the baseline questionnaire that was used to recruit participants (with HE-B, SP and MO) and included a UWL section with screening questions for which I was solely responsible. I collected baseline data for the PACE database with two other PhD researchers (HE-B and SP). The participants' primary care records were then subjected to a second case note review. I combined the PACE study baseline and UWL data into one dataset. I designed the analysis plan for the quantitative data and conducted the analyses.
3. I designed the interview topic guides (Appendix 7) used for the semi-structured interviews, recruited the patients whom I had I interviewed using the PACE study baseline data, and coded and analysed the qualitative data collected from those interviews. A dietitian doctoral research colleague (AB) and one of my PhD supervisors (MJ) did some secondary coding of a subset of interview transcripts, which contributed to the development of the coding frame and early themes.
4. Finally, I integrated and analysed the quantitative and qualitative data collected in the previous two phases.

3.8 Study phases and research methods

3.8.1 Phase I: Systematic review of the literature

Before recruiting participants as part of the PACE evaluation, a systematic review of the literature was conducted to categorise tools and methods used to screen and assess cachexia in patients by healthcare setting. This review was conducted to establish in which settings that cachexia studies take place and particularly how it is screened and assessed in primary care settings. Due to the exploratory nature of the review, a narrative synthesis was used to describe the results. This study phase answers research question one (RQ1 - What tools or methods are used to identify

and assess cachexia symptoms and in which healthcare settings?) and is described in detail in Chapter Four of this thesis.

3.8.2 Phase II: Quantitative research study

3.8.2.1 Cross-sectional survey methods

A cross-sectional survey is a quantitative data collection method, which is used to describe and make inferences about a population of interest at a single time point or time frame (177). In contrast, longitudinal studies can employ a series of questionnaires or surveys to collect data over a longer time period. Cross-sectional surveys can be conducted in several ways—they can be administered to an entire population or a subset of a population. Surveys can also be administered in person or over the telephone. The survey can also be self-administered and accessed through postal or email invitations or internet-based data collection tools (178).

The majority of cross-sectional surveys are conducted with a subset that is representative of the population in question for practical purposes, rather than the whole population. Common sampling techniques include randomly selecting a sample (probability sampling technique), systematically selecting a sample (e.g. picking every tenth participant in a sample), and selecting a sample using stratification to ensure that prespecified subgroups of the population are represented (177). The chances of bias are reduced when randomised sampling techniques are employed. Furthermore, the external validity of the study (i.e., how generalisable the findings are) is improved when selecting a sample randomly.

Data collected using cross-sectional surveys can be descriptive, such as data used to assess the prevalence of a disease/condition and details of possible risk factors can be collected at the same point in time. Cross-sectional survey data can also be analysed to assess the association between a disease/condition and risk factors. However, as this type of data concentrates on participants' current status with respect to risk factors and disease outcomes, the temporal relationship between the two cannot be determined, and one can only presume that the variables are

related or assess the frequency of occurrences across groups or population characteristics (177).

A cross-sectional survey was the quantitative research method chosen to describe the PACE study participants at baseline (Appendix 1). The clear advantage of using this study design is that a large number of participants can be asked a set of standardised questions to obtain descriptive quantitative data at a specified time point (the day of their ICC assessment). This was both a descriptive and analytical cross-sectional survey. The prevalence of self-reported UWL was calculated using descriptive data. The baseline questionnaire had a section with screening questions to elicit this information. Analytical methods were used to assess population characteristics across groups (for instance, those who self-reported UWL and those who did not).

The participants were recruited using consecutive sampling, in which anyone ≥65 years who had attended the ICC was offered the opportunity to participate in the PACE study until 300 participants were recruited. The ICC multidisciplinary assessment was available to those at risk of severe frailty, of all ages. The PACE study participants, however, were aged 65 years and over, Figure 2. Consecutive sampling was a pragmatic choice that enabled the research team to approach all patients who met the age requirements, while causing minimal disruption to the flow of the clinic processes. As previously stated, although this type of sampling is similar to convenience sampling and is not a randomised sampling strategy, it is preferable to purposive sampling for reducing sampling and selection bias (179, 180). It permits all individuals who meet the inclusion criteria to be approached, rather than relying on the researcher's judgement or discretion (178).

As part of the recruitment process in the clinic, clinic staff and caregivers were able to guide the research staff if patients were amenable to being approached but lacked mental capacity. Before their multidisciplinary assessment date, participants were sent the patient information sheet alongside their ICC/intervention invite by the clinical team to provide enough time for them to

consider participation and informed consent. Participants and any caregivers in attendance were approached by the clinical team at the time of their appointment and then – if willing to participate – were consented by a member of the study team. These touchpoints were important to allow for informed consent and to determine the mental capacity of any potential participant. The study consent form and baseline questionnaire were adapted for patients with impaired mental capacity to participate. If impaired mental capacity was determined, using this approach, then the adapted consent form was completed by a proxy (a family or formal caregiver) who had been approached before and at the time of the ICC assessment. The baseline questionnaire was then completed with the cooperation of the participant and or their proxy. This approach was required as the study team were aware that selection bias could be introduced if potential participants in this age and patient group were excluded on the grounds of impaired mental capacity. Additionally, this approach allowed for professional caregivers at the care homes to be proxies with the approval of the next of kin. Importantly, the study team did not approach patients identified as lacking mental capacity who were alone and had no proxy (formal or family caregiver). The ethical considerations of including participants lacking or with impaired mental capacity are described in Section 3.9 of this thesis.

Another advantage of using this study design was that the paper survey could be administered to participants and caregivers, but it was also designed so that participants could complete it themselves if they preferred. There was some recall bias in this study design, as the survey required participants to self-report and recall information. However, this was a data collection tool used at baseline that also gave the researchers an opportunity to gain consent to access the participants' clinical records. The case note review enabled the researchers to either validate the survey data or reduce patient burden by reducing the number of questions asked of the participants (such as details of co-morbidities, prescriptions and details of GP appointments in the previous 12 months).

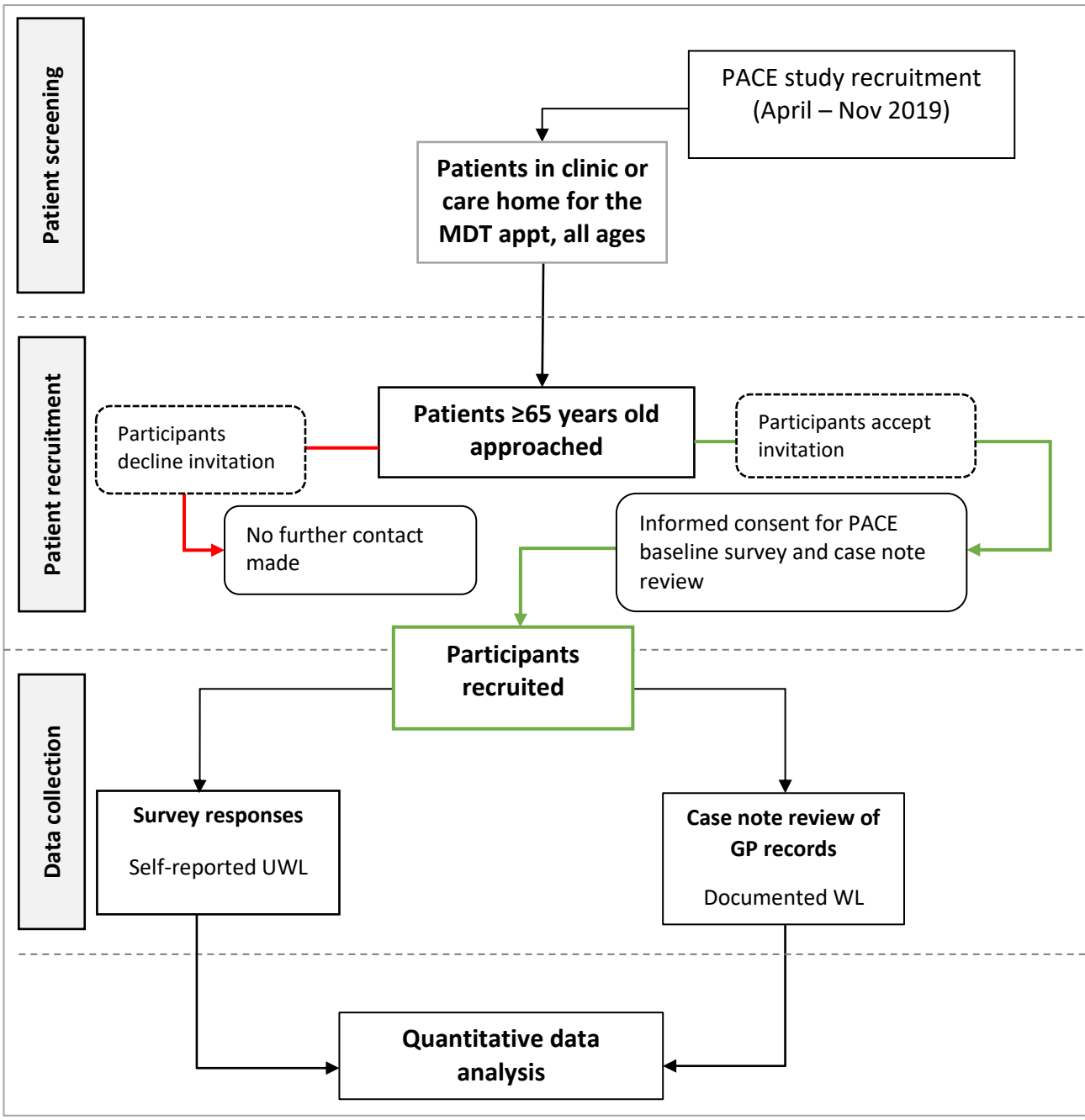


Figure 2: Patient recruitment process

3.8.2.2 Case note review methodology

Case note review is a retrospective quantitative research method known as chart review, medical record review, retrospective chart review, chart audit and case note audit. Retrospective reviews of patient records are commonly used in healthcare audits, evaluations and research (181). The review can involve the whole patient record, all the data from a specific patient admission (the 'index' admission) or data

extracts from the whole record. Reviews of medical records from electronic systems and databases, rather than paper records, are increasingly common. These reviews can involve data mining and the use of data algorithms to retrieve patient-level data (182).

Case note reviews are used to collect information on the following (182, 183) :

1. Determining the clinical characteristics of diseases
2. Studying the course and outcome of diseases over a follow-up period.
3. Attributes of a patient population accessing a service.
4. Adverse events and medical errors
5. Surveillance of health issues and risk factors or indicators

Case note reviews can be explicit or implicit (also known as holistic case note reviews). Explicit case note reviews use frameworks of predetermined criteria or clinical guidelines and tend to follow on from a literature review (182). Holistic case note reviews have been used to assess the safety and quality of care for certain conditions and time periods. They tend to be more nuanced, rely on clinical judgement and are good for reviewing hospital mortality cases (181). Holistic case note reviews have been criticised for their low inter-rater variability, and there is a higher potential for reviewer bias (181). (181)

A case note review was used in this PhD project to reduce the patient burden of the information needed from the PACE study's baseline survey. This was an explicit case note review, as it was based on findings from an initial scoping study and then a systematic literature review on how cachexia is assessed in patients with chronic and end-stage diseases (reported in Chapter 4). A case note review proforma was used by three researchers for the PACE study data collection. I developed a separate proforma for my sole use for an additional review of the records for weight measurements, weight loss assessment and management in the electronic primary care records of PACE study participants (see Appendix 2 for both proformas).

The advantages of case note reviews include reducing the patient burden on the number of questions in the baseline survey and, thereby, limiting recall bias. As I was unable to conduct interviews with healthcare professionals as planned, the case note review became more significant, as it represented the only opportunity to collect data from the perspective of healthcare professionals in a primary care setting. The disadvantage of case note reviews is that the quality of the review can depend on the quality of the case notes. Case notes can be missing from paper records and electronic health record systems, and data might be missing or incorrectly recorded in notes that are accessible. Persistent documentation errors are also an issue in which data are initially incorrectly recorded in one entry (e.g. patient demographics), or measurements and vital signs are incorrectly calculated or recorded (e.g. BMI) but are then persistently replicated in consecutive appointments. There is the potential to address this type of documentation error when reviewing the whole patient record, but it is a limitation when data extracted from the notes or a specific time period are being reviewed. Other limitations exist when there is more than one reviewer, and there is no agreed data extraction process or data extraction form (184) or an agreed way to treat missing data (185). The quantitative data collection process is described in the next section.

3.8.2.3 Quantitative data collection

The purpose of this study phase was twofold: (1) to describe and compare the characteristics of older patients attending an integrated care clinic who reported UWL in the previous 12 months using a baseline questionnaire and (2) to conduct a case note review of the participants' primary healthcare records to assess the degree of weight loss and if their objective weight loss was assessed and investigated in primary and community healthcare settings. Research questions 2 to 14 are answered by this study phase, and the results are described in Chapter Five of this thesis.

The baseline questionnaire was administered at the newly established integrated care clinic for patients with frailty to identify a patient cohort who had experienced UWL in the previous 12 months. The patients were approached by the research

team in the waiting room of the ICC while they were waiting for various assessments on their 'patient journey' in the clinic. If amenable to participating in the ICC evaluation (PACE study), we obtained informed consent and administered the baseline questionnaire (Appendix 1). Each clinic day was scheduled to evaluate a maximum of eight patients, and it took three months to recruit ICC participants for the PACE study (May–August 2019). The recruitment process for care home participants involved four care homes and lasted three months (September–November 2019). The recruitment at the care homes differed since the ICC multidisciplinary team visited the care homes weekly in a rotation. They would go through the list of eligible patients (eight a day), discuss each case with a deputised senior care assistant, and then they would visit the patient (accompanied by a relative, if available) to see them and further discuss their needs. A member of the research team was present for the initial discussions and was advised by the care assistants about which patients were happy to be approached. When consent was given, the research team administered the baseline questionnaire to the patient or one of the senior care assistants responsible for their care.

All study participants were given a baseline questionnaire with screening questions. They were asked further questions about their weight loss and any loss of appetite if they initially reported losing weight unintentionally. They were also asked by whom they had been weighed in relation to their UWL and whether they had received advice or treatment to gain weight.

The second phase of the quantitative data collection was the case note review of PACE study participants who had consented to the researchers accessing their primary care records. An electronic healthcare record system was accessed, and a proforma was used to collect further information for each participant (Appendix 2). Details of appointments were extracted if they had happened within the previous 12 months before the patients' ICC assessment. The electronic health records were reviewed for weight measurements (with or without a BMI), the date weight was recorded, the type of healthcare appointment the weight was recorded, and the healthcare professional who entered the weight measurement.

The following measures were included in the baseline questionnaire and case note review proforma to aid in describing the characteristics of the PACE study cohort (Appendix 3):

1. Quality of life was measured using the EuroQol- 5 Dimension (EQ-5D-5L) (186)
2. Functional status was measured using the Australian Karnofsky Performance Status (AKPS) (187)
3. Patient well-being, as measured using the Integrated Patient Outcome scale (IPOS) (188). The quantitative phase of this PhD project utilised the IPOS appetite score.
4. Frailty was measured using the Rockwood Clinical frailty scale and the electronic Frailty Index (131).
5. The number of comorbidities per patient were counted using the Adult Comorbidity Evaluation-27 (189). The ACE-27 is a 26-item list of comorbidities for people with cancer. It is partly based on the Charlson Comorbidity Index but adds a number of conditions (including obesity) and puts more emphasis on cardiovascular disease. The scoring system, when used, will lead to an overall morbidity score which is the 27th item. The list of comorbidities uses "history of …" symptoms/ conditions which is especially important for cancer as it might relate to UWL. Using this list removed some of the more commonly noted but not as impactful cancer diagnoses like basal skin cancers.

3.8.2.4 Quantitative data analysis

The quantitative analysis research questions were answered using themes—the characteristics of patients with self-reported UWL and how they compare with patients without self-reported UWL. The characteristics of patients with documented weight loss and how they compare with patients without documented weight loss; the association between self-reported UWL and documented weight loss; and the characteristics of patients with weight loss measurements and management of UWL compared to those without.

Data from the baseline questionnaires and health records were integrated into one spreadsheet and exported to statistical software (SPSS v27) for analysis (190). Descriptive statistics (proportion, mean, median and inter-quartile ranges [IQR]) were used to analyse and describe clinical and demographic data and the clinical and demographic characteristics of the study population. Means and standard deviations were used to describe normally distributed data, and medians and IGR were used for skewed data. The categorical data were described by percentages.

Inferential statistics were used to compare differences between the participant groups. Participants who reported UWL had significant documented weight loss and those who had a management action for their weight loss recorded in their notes were compared with those in the study population. A 'management action' was a composite measure that reflected the presence of one or more of the following in the case notes during the previous 12 months: an assessment of appetite or nutrition, an investigation ordered in primary care (blood test, scan or x-ray), a referral to other healthcare service for further investigation or treatment, or a treatment to address the weight loss (e.g. dietary supplementation).

Differences between groups were tested using independent samples t-tests for continuous data variables, Mann-Whitney U for skewed continuous data variables, Fisher's exact test for binary categorical variables, Pearson's chi-squared test for data with more than two nominal variables, and McNemar's test to compare categorical paired data.

Logistic regression models were constructed to assess the relationship between patients' demographic and clinical characteristics and the following (Appendix 14):

1. Documented significant weight loss in their health records (RQ 6)
1. A self-report of unintentional weight loss (RQ 8)
2. A management action for significant weight loss documented in their health records (RQ 14)

The above variables are binary outcomes, so binary logistic regression was used as an appropriate regression model. Univariate logistic regression models were first run with all the independent variables described in the descriptive analyses. Independent variables were included in a multivariate logistic regression model if their univariate models had a *p*-value less than 0.25 (191, 192), if they were of clinical significance (according to clinical definitions) and if they had a *p*-value more than 0.25. The model was re-run with independent variables removed using a stepwise analysis with backward elimination until all remaining variables were significant (*p*-value less than 0.05).

3.8.3 Phase III: Qualitative research study

3.8.3.1 Qualitative interview methodology

Qualitative interviews were conducted to elicit the views and experiences of study participants. There were also plans to recruit a range of healthcare professionals as participants but these proved to be challenging due to autumn/winter pressures in 2019 and the COVID-19 pandemic in early 2020. Therefore, qualitative interviews took place with PACE study participants. Interviews can be used to understand the participants' behaviour, decision-making and beliefs and practices. Qualitative interviews can be (1) structured with a fixed schedule, closed questions and no variation; (2) semi-structured - where an interview schedule is used but with prompts and follow-up questions; or (3) unstructured, which is more of a free-flowing interview with open-ended questions(177). The level of structure will affect different aspects of the data analysis – structured interviews emphasise on reliability, allowing for easier comparisons between different interview responses. This standardisation of the interview process generates responses that can be coded and analysed quickly (177). Interviews that are less structured place more emphasis on validity, where understanding the world from the interviewee's or respondent's perspective is prioritised by allowing flexibility in the interview schedule (193). In less-structured interviews, the respondent is allowed to direct some of the focus of the conversation. Furthermore, the interviewer's and respondent's interactions are more accessible, while the interviewer considers their neutrality concerning the participant (194).

The strengths of a semi-structured interview are that they are 'conversations with a purpose' (195) where the interviewer builds rapport with the respondent to enable a freer conversation while still covering a core list of questions and topics (177). The interviewer makes decisions about the general direction of the conversation while allowing tangents to occur (177). Conducting semi-structured interviews provides an opportunity to collect in-depth data without the time and resources needed to conduct fully open and in-depth interviews (194).

Other qualitative methods that could have been used included focus group interviews and participant observation. Semi-structured interviews, as a methodological approach, were more convenient for this patient group. Focus group interviews would have been difficult to arrange with participants and caregivers, and some participants would have been hesitant to openly discuss sensitive health-related topics in the presence of strangers. In planning the PACE study, the research team visited the ICC and followed some through their assessment journey. We saw that there would have been an opportunity to conduct participant observation while shadowing patients through the clinic. However, this would have placed more emphasis on observing interactions with the ICC staff and the processes in the clinic rather than focusing solely on the patients' thoughts, experiences and feelings. It would also be difficult to openly discuss sensitive topics in ICC waiting areas and consultation rooms. Participant observation in the patients' homes would also have been unrealistic. Only one researcher was conducting these interviews, and it would not have been feasible to spend the amount of time needed to observe participants in their homes and generate similar levels of data as interview data. Additionally, it would have been challenging to recruit participants for this level of intrusion/observation in their private lives. I also did not have the time to process and analyse field notes and interview data that would have resulted from extensive participant observation.

3.8.3.2 Qualitative data collection

Patients who had experienced UWL were invited to participate in the qualitative phase of the study. Purposive sampling was initially planned but with the recruitment challenges experienced (see Section 6.3 and Section 8.4) convenience sampling was used to recruit the patient/family caregiver participants. Semi-structured interviews were conducted to elicit the views and experiences of patients and their family caregivers on their weight loss, how it has been assessed, and what guidance they have received from healthcare professionals, Appendix 7. This study phase answers RQ15: What are the experiences of patients (and caregivers) with UWL of their symptoms and of the assessment and management of their symptoms in primary care? The results are reported in Chapter Six of this thesis.

Semi-structured interviews were conducted with a convenience sample of participants who reported UWL in the baseline questionnaire and who were willing to participate when approached for an interview. If a family caregiver accompanied the patient, they were also asked if they would be willing to be interviewed. Interviews were conducted in the participants' homes at a convenient time for the interviewer, participant and family caregiver. Where possible, the majority of family caregivers and participants were interviewed.

Before starting the interviews, written informed consent was obtained and recorded on a digital recorder. The interview schedule was divided into four main areas of enquiry: the patient's health status, details and experience with UWL, the experience with appetite loss, help-seeking and healthcare professionals' expectations. The interviews took approximately 45–60 minutes for each participant or patient/family caregiver participant duo.

For accuracy, I transcribed the interview recordings verbatim and checked the transcripts against the audio recordings. Each transcript was then anonymised to conceal the identities of the participants. This was achieved by removing or changing any information that could be used to readily identify participants, such

as people's names, geographical areas and places of work. All transcripts were transferred into NVivo, qualitative data analysis software for coding. I used QSR International's NVivo 12 software to code the entire dataset and generate initial codes (196). The codes were collated into potential themes. To ensure consistency, a proportion of the interviews were also coded by one of my PhD supervisors (MJ) and a PhD colleague who is a research dietitian (AB). The coding was conducted separately, followed by a brief discussion to discuss the coding framework and any similarities and differences. There were very few differences and gaining different perspectives on the data through these discussions contributed to the development of the coding frame and early themes. I discuss this further in the next section.

3.8.3.3 Qualitative data analysis

A range of analytic methods can be adopted to analyse qualitative data (e.g. interpretative phenomenological analysis, discourse analysis, grounded theory and thematic analysis). The analysis method chosen for the qualitative data in this study was reflexive thematic analysis. Thematic analysis is an underpinning analytical approach used for qualitative analysis methods such as grounded theory, phenomenology, case studies and narrative analyses. Thematic analysis has been described as a method of 'identifying, analysing, and reporting patterns (themes) within data' by Braun and Clarke. They have helped establish it as a qualitative analytic method in its own right (197).

The analysis of the qualitative data followed the phases as described by Braun and Clarke (197): data familiarisation, initial code generation, generating initial themes, theme review, theme defining and naming and report production:

- Data familiarisation: Immersion in the data to understand the depth and breadth of the content through transcribing the audio data, reading and re-reading the dataset and taking notes. This was the beginning of the process of identifying patterns and meanings.

- Initial code generation: Generating the initial codes, organising data by labelling and managing data items into meaningful groups
- Generating (initial) themes: Sorting codes into initial themes and identifying the meaning of the codes and the relationships between the initial codes. This was accomplished by mapping and defining the properties of the themes.
- Theme review: Identifying patterns at the coded data level and reviewing the entire dataset; this theme review was facilitated by collapsing overlapping themes and re-working and refining codes and themes.
- Theme defining and naming: Identifying the story of each theme and fitting it into the broader story of the dataset to respond to the research questions. This involved cycling between the data and the identified themes to organise the story.
- Report production: Presenting an account of the story told by the data, both within and across themes, the end result is intended to be a write-up of a compelling argument that addresses the research questions that is more advanced than a simple description of the themes (197).

Most of the reflexive thematic analysis phases, above, were conducted iteratively over and beyond the data collection time period as the interviews were conducted and the interview data transcribed. The initial codes, coding framework and early themes were discussed in supervisory meetings. These meetings were also opportunities for debriefing after recent interviews to discuss and get guidance on the interview process. It was also an opportunity to discuss any distressing or sensitive research findings. Separate and more formal, debriefing meetings took place with my second supervisor (MJ) and PhD colleague (AB). Four interview transcripts were shared with both for independent review and for them to code. I met with MJ once and with AB twice to discuss the data, their initial thoughts as to codes and themes. As healthcare professionals - AB is a dietician and MJ is a consultant palliative physician, both were also able to provide me with some professional insights and context. I recorded the meetings with AB with her

consent and reviewed the transcripts on several occasions. I also met with a visiting Professor and a researcher to the University department to discuss my quantitative and qualitative data in January 2020. It was useful to obtain an external review of the data I was collecting. I also, periodically, recorded voice memos to document my reflections post interview and during the data analysis process.

The voice memos, notes and discussion points from all meetings helped shape the development of the coding framework and early themes. The process allowed me to see patterns and themes from different perspectives and made more alert to follow up questions that I could ask in the remaining interviews. The reflexive thematic analysis phases – 'theme review', 'theme defining and naming' - then occurred iteratively with input from my supervisors during our monthly supervision meetings.

The use of reflexive thematic analysis is appropriate in this study due to its flexibility. It can be used across several disciplines and can be used flexibly with different theoretical approaches (197, 198) or it can be fixed to more realist or positivist paradigms (199). As an analytic method, themes can be generated deductively (where themes relate to a predetermined model or theory) or inductively (from the data) (200). This study was conducted without a predetermined theoretical coding framework, as this study's elements were exploratory. Thus, the themes were derived from the raw data, which meant that they could deviate from the questions asked of the participants.

Braun and Clarke (201) describe four variations of reflexive thematic analysis, which can be dichotomous but where some of the dimensions can overlap:

1. Orientation to data: inductive versus deductive
2. Focus of meaning: semantic versus latent
3. Qualitative framework: experiential versus critical
4. Theoretical frameworks: realist, essentialist versus relativist, constructionist

In accordance with the specified variations, I positioned this qualitative study as follows:

Inductive (the analysis was located within coding and theme development from the data) rather than deductive—where the analysis is shaped by theoretical frameworks, which then drive data coding and theme development. The focus of meaning was *semantic* (where the analysis explored meaning at the more explicit or surface level), which is ideal for an exploratory, descriptive study. Latent meaning is where the analysis is more implicit and explores the underlying meaning of the data, leading to the development of theory, which may require some abstraction from the data. The qualitative framework, as a variation of the reflexive thematic analysis described above, was *experiential,* where the analysis aimed to capture and explore participants' perspectives and understandings. In contrast, a critical qualitative framework was created where the analysis unpacked meaning around the topic area and organised the participants' contributions to the topic or issue. The theoretical framework this study leaned towards was *realist, essentialist*—where analysis aimed to capture the reality of truth as expressed in the data. A relativist, constructionist framework, in contrast, aims to unpack the meaning behind the realities expressed within the data. This leads to attempts to understand the social construct of meaning expressed by participants, as there is no objective reality but reality manifested by individual and societal sense-making.

Another strength of using reflexive thematic analysis is its reflexivity. Braun and Clarke incorporated the term 'reflexive' to allow the researcher to position themselves in the analysis of the data (197). Reflexivity for the researcher involves drawing upon their pre-existing knowledge, experiences and aspects of their social position (such as ethnicity or gender). The researcher is able to 'critically interrogate' how the above factors influence and contribute to the data analysis and interpretation of the qualitative data (201). This methodology invites the researcher to explore and make explicit their values, personal insights, perceptions about the world and beliefs (ibid.). Reflexive research requires that knowledge be treated as situational, such that it is always a consequence of an interaction between the researcher and the data (ibid.). I used reflexive thematic analysis

because it afforded me the opportunity for reflexivity as I had witnessed a close family member experience UWL due to cachexia. This is explored and reported in Section 6.10.

3.8.4 - Phase IV: Integration of the quantitative and qualitative results

3.8.4.1 Data integration

As outlined in Figure 1, data integration in this study design occurred at three time points: using the quantitative findings to guide the qualitative sampling, cross-referencing some of the quantitative findings with the qualitative interviews and data analysis, where findings from both phases were integrated. The last two data integration approaches were used to answer RQ 16: How is UWL assessed and managed in primary care, and experienced by older patients who might be at risk of developing cachexia? All the results and themes from study phases two and three were brought together to provide an overview of how UWL is identified and managed in primary care in patients at risk of developing cachexia.

Both qualitative and quantitative data sets were first merged into a single database for the subgroup of participants who were enrolled in both the quantitative and qualitative phases of the study (n = 15) to attempt to visualise an integrated view of their experiences with UWL. This initial data integration was then analysed using a triangulation protocol devised by Farmer et al., who suggested using a converging coding matrix in qualitative data studies (202).

Farmer et al. suggested a six-step triangulation protocol and used it for three types of triangulation:

1) Multiple investigators: where researchers in a research team applied the triangulation protocol independently and compared the results.
2) Methodological: where results were compared from two methods of data collection.
3) Data source: where a range of project perspectives were represented in the interview analysis and a range of project documents are reviewed.

This approach was further adapted for use in mixed methods research by O'Cathain et al.(203). I used the first four steps of Farmer et al.'s six-step triangulation protocol to integrate and analyse the mixed methods data Table 6, and the findings are reported in Chapter 7. The first steps of the triangulation protocol describe the practicalities of how the data can be integrated and analysed. In addition to that, however, Farmer and colleagues have developed the protocol to allow researchers to develop 'meta-themes' that move away from considering the findings from different methods sequentially—they cut across the findings from different methods and can then be interpreted in a more global fashion (202).

Table 6: Triangulation protocol with a converging coding matrix

1. Identify cases (PACE study participants who are interview participants).
2. Data extraction: for each interview participant, list together qualitative and quantitative findings.
3. Convergence coding: Develop a convergence coding matrix based on the specific research questions. The rows of the matrix represent the identified themes, and the columns describe the various levels of convergence. *Agreement:* full agreement between the sets of results on both elements of comparison *Partial agreement:* There is agreement on one but not both components. *Silence*: One set of results covers the theme, for example, while the other set of results is silent on the theme or example *Dissonance*: There is a disagreement between the sets of results on both elements of comparison
4. Convergence assessment and interpretation: to identify the global assessment of the level of convergence (whether the findings suggest convergence, complementarity, discrepancy, or dissonance.)

Adapted from Farmer et al. (202) and O'Cathain et al. (203)

3.8.4.2 Framework used for mixed methods data mapping

After data integration and analysis, an adapted framework using Andersen's model of total patient delay was used to map the main themes and findings (204). The main focus of the original model was on how symptom appraisal and health-seeking behaviour can lead to a delay in cancer diagnosis. The model describes a multi-stage pathway from the onset of symptoms to the diagnosis and treatment of cancer. The pathway is generally regarded as having two main phases: one that reflects the time it takes for the patient to appraise their symptoms and seek medical attention, and the other is the diagnostic phase that is dependent on the

patient's journey through the healthcare system. Andersen et al. conceptualised delay intervals as occurring between the phases of decision-making or the components of delay. Delay is comprised of five stages: appraisal, illness, behavioural, scheduling and treatment delay intervals (204):

1. Appraisal delay refers to the time taken for the patient to interpret symptoms as an illness after they have been detected.
2. Illness delay is the time the patient takes to decide that the illness needs medical attention.
3. Behavioural delay describes the time between the patient concluding that the illness requires medical attention and deciding to act on this decision.
4. Scheduling delay describes the time taken to act on the decision to seek help and actually attend an appointment.
5. Treatment delay refers to the time between the first appointment with a healthcare professional and the start of treatment.

Patient delay is often influenced by behavioural, psychological and socio-demographic factors as well as symptom awareness (205, 206). In qualitative studies, Andersen's model of total patient delay has been used to investigate how cancer symptoms are detected and what prevents patients with suspected cancer from seeking medical care (207-211). It was felt that this model would be an appropriate framework for attempting to map the pathway from onset to the assessment, investigation and management of UWL. This was due to the similarity in the diagnostic pathway, in that UWL can be a symptom that leads to a cancer diagnosis. However, the pathway was adapted to reflect the journey in primary care only and not the referral and diagnostic stages seen in the original Andersen model. Furthermore, mapping the quantitative findings and qualitative themes provided an additional method for integrating the two datasets and conceptualising and describing factors that lead to patients and caregivers seeking healthcare interventions for UWL.

3.9 Ethical considerations

This research study involved human participants recruited from the NHS setting. Therefore, there were a number of ethical considerations that needed to be addressed to conduct this study.

An application was submitted to the HYMS ethics committee, as guided by the Hull York Medical School (HYMS) postgraduate researcher guidelines. HYMS ethics committee approval was received for the PACE study protocol and study documents in October 2018. On 24 January 2019, NHS Research Ethics Committee (REC) approval was obtained for the PACE study (REC reference: 18/YH/0470), Additional research governance approvals to access specified NHS sites and staff were received from the HRA (22 March 2019), the City Health Care Partnership's Research Approval Group (13 April 2019) and Hull Clinical Commissioning Group (14 April 2019). All of the above approvals can be seen in Appendix 4.

As permitted by NHS REC processes, I emphasised the voluntary nature of participation when recruiting participants. Participants were given copies of REC-approved information sheets and consent forms in Appendices 5 and 6. During an informed consent process, participants were informed why the PACE study was being conducted, why they had been approached, how we would collect and store data, how we would preserve their anonymity, how the results would be disseminated and that they could withdraw from the study at any time.

In recruiting older adults with moderate to severe frailty, the study team determined that it was important to consider their capacity to participate. Older adults are living with more chronic conditions, multi-morbidity and frailty, and may have cognitive issues that influences their capacity to consent to study participation. In line with the ethical principle of autonomy, only relevant questions were included in the baseline questionnaire so as not to overwhelm the patients with unessential detail (212). All study materials were written in accessible language. The capacity of potential participants were discussed with the clinical team and with caregivers to help identify patients with possible capacity issues. In

line with the Mental Capacity Act (213) capacity was assessed in a three-stage process to: 1) determine if the individual could understand the information provided about the study; 2) retain the information (even for a short time); and 3) use or weigh up that information and communicate their decision.

To summarise, three approaches to consent were used:

1. For patients with capacity, consent was taken at baseline and checked with each further contact. Additional consent was sought if they were approached for qualitative interviews.
2. For patients with impaired capacity, consent was taken in the moment, with the aid of a proxy, at baseline. Consent was sought at subsequent data collection points from the participant and their proxy.
3. The study team did not approach patients identified as lacking capacity who were alone and had no proxy (formal or family caregiver).

Throughout the study, data were collected, processed and stored in accordance with HYMS guidelines and NHS REC approval. Each participant was assigned a study ID number for data entry into the study database, which was used instead of personal identifiers. The anonymisation continued in the storage of the audio files of the interviews. The audio files were saved with study ID numbers, and the transcriptions removed any identifying references to names, addresses, local health services and other identifiers. All databases, audio files and transcripts were saved on password-protected files in a study folder on a university network that was only accessible to the research team and those legitimated to review governance processes for audit or quality standards.

In addition, care was taken in the study's design to minimise harm and distress. Cachexia is a very distinctive term. There was concern that it could be an upsetting discovery if patients and their families were to research what it meant. It was not the researcher's responsibility to reveal the nature of the condition to the participants for the first time. Therefore, I inquired about 'unintentional weight loss' and omitted cachexia from the information sheets and consent forms. When participants were recruited at the ICC, they were introduced to the study during

the pre-assessment visit, and they received additional information while waiting in the ICC room. Patients were given information about the study so that they could decide whether or not to participate, and they were given the opportunity to ask questions. In addition, a safeguarding procedure was in place for the researchers to report participant interactions to the ICC. Any concerns uncovered through administering the baseline questionnaire and conducting interviews were communicated back to the ICC staff with the patient's consent. Information sheets also included a telephone number and email address for the participants to contact if they had issues or questions with the study or its conduct.

3.10 Summary

This chapter (Chapter 3) provides an explanation of the methodology used for this mixed methods study. The chapter began with an overview of the study aims and objectives, followed by a list of the research questions. A description of the research focus was provided, followed by a definition of the methodology. As part of the methodology description, I described the philosophical framework, the rationale for using mixed methods and the sequential explanatory mixed methods study design.

The chapter provided descriptions of the study phases, including the systematic review (Phase One), quantitative and qualitative phases (Phases Two and Three), the recruitment method for Phase Two, the participant selection used in Phase Three, and methods, data collection and data analysis for each of the mixed methods phases. In addition, the integration and analysis of the mixed methods of research findings (Phase Four) were explained along with the ethical considerations for the study.

The methods used for the systematic review of the literature and the findings of the resulting narrative synthesis are presented in Chapter 4.

4 Systematic literature review

4.1 Introduction to the systematic review

This chapter describes the methods used to systematically search the literature to outline the methods used to identify cachexia in patients with chronic conditions and malignant diseases in studies published from 2008. The literature review answers the first research question: What tools or methods are used to identify and assess cachexia symptoms and in which healthcare settings? The results of the searches were incorporated into a narrative synthesis from which a number of themes were produced. The healthcare contexts where the research was conducted were also described in addition to the list of methods used identify cachexia.

4.2 Background

Cachexia is a multifactorial metabolic syndrome which includes UWL and is most commonly associated with advanced disease states such as cancer, chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA) and chronic kidney disease (CKD) amongst others (23, 48). Associated symptoms include loss of appetite, muscle weakness and fatigue. Cachexia has been reported as being prevalent in 5-15% of patients with CHF and 50-80% of patients with advanced cancer (42, 48, 214).Compared with other types of weight loss, cachexia is irreversible with nutritional support alone (9). Systemic inflammation or tumour cell proliferation driven by the underlying disease state can lead to disordered metabolism which in turn leads to a predominant breakdown of muscle (24). Weight loss can be worsened by a loss of appetite secondary to the pro-inflammatory state, treatment received, other chronic conditions, associated prolonged immobilization and a deterioration in physical function (9).

An often-stated challenge in managing and identifying cachexia has been the absence of a standardised definition. Early diagnostic criteria referred to weight

loss in a specific time period but without an associated change in body tissue composition (11). Overarching diagnostic criteria were published in 2008 by Evans et al. (8). The Evans' criteria defines cachexia as weight loss of at least 5% in the past 12 months or less in the presence of underlying disease and three of the following: decreased muscle strength; anorexia; fatigue; low fat free mass index; and abnormal biochemistry (8).

In recognition that the clinical presentation of cachexia varies by disease, more specific diagnostic criteria have since been published. Cancer specific criteria were developed by Fearon et al. in 2011, for CHF by Anker in 2003 (215) and RA by Engvall in 2008 (216) and others are in development, e.g. a cachexia phenotype for end-stage renal disease (20). The diagnostic criteria proposed by Fearon et al. define cachexia as an involuntary weight loss over 5% of normal weight in the past 6 months; or weight loss over 2% and BMI less than 20 kg/m^2; or weight loss over 2% with decreased muscle mass (sarcopenia) (9). This contrasts with rheumatoid cachexia where there may be a change in body composition (decreased muscle mass) that may be undetectable due to a normal or high BMI and no measurable weight loss (217, 218).

An additional complication in detecting cachexia symptoms is that they overlap with those of common chronic diseases, malnutrition, and age-related weight loss due to muscle loss (sarcopenia) and physical frailty. Weight loss due to malnutrition can be a component of both sarcopenia and cachexia, especially in the frail older patients. Malnutrition screening tools are commonly used to detect weight loss from a number of causes but there is currently only one validated screening tool for cachexia and two for sarcopenia (219). Publications have addressed the interplay of cachexia, sarcopenia and malnutrition by suggesting the creation of a novel screening tool that can simultaneously detect the three syndromes in a stepwise manner (219) and by the development of a diagnostic framework for malnutrition that overlaps the other two syndromes (220).

While these consensus definitions and criteria exist, the current challenge is that little is known about how they are used in clinical practice. The aim of this review was to systematically search the literature for primary research studies where participants had been assessed for cachexia and to describe the healthcare contexts of the studies, the assessment methods used, and the diagnostic criteria employed.

4.3 Methods

The systematic review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO CRD42018087087). This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (221).

4.3.1 Inclusion and exclusion criteria

Primary research studies using quantitative or qualitative methods were eligible for inclusion. Randomised controlled trials (RCTs), non-RCTs, cohort studies, observational studies, cross-sectional studies, and before-and-after studies were included. Case reports, case series, and literature reviews were excluded. The studies were in health care settings rather than laboratory based.

Studies that recruited adult patients with chronic conditions and malignant disease were eligible for inclusion. Patients in these studies were assessed for cachexia induced weight loss related to those disease conditions. Studies were excluded if the weight loss was due to sarcopenia, malnutrition or disorders leading to muscle wasting without reference to cachexia in this patient population.

Publications from 2008 to August 2022 were eligible and only English language studies published in peer reviewed and grey literature were included. Exclusions were also made if the weight loss was due primarily to malabsorption associated with trauma, surgery, inflammatory bowel disease or coeliac disease. Studies were also excluded if there were physical factors that impaired dietary intake, if patients

had reversible causes of malnutrition, weight loss due to psychiatric disorders and cachexia associated with HIV/AIDS (normally reversible with antiviral therapy). The year 2008 was chosen as the start date of the review as this was the year that the first diagnostic criteria for cachexia was published - Evans et al. (8). Additionally, this coincided with a decrease in publications in HIV/AIDS-related cachexia.

4.3.2 Outcomes of interest

Methods and tools used to screen or identify weight loss or symptoms due to cachexia such as nutritional or cachexia-specific screening tools were listed and where possible, healthcare settings in which screening and identification of cachexia took place were described.

4.3.3 Search methods

A systematic search of the following electronic databases was conducted: Cochrane Database of Systematic Reviews (CDSR); Database of Abstracts of Reviews of Effects (DARE), MEDLINE via OVID, EMBASE via OVID, PsychINFO via EBSCO and Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete via EBSCO. The databases were searched for journal articles published from 2008 to 31st August 2022. The search comprised of a combination of MeSH terms and key words that reflected key components – (1) cachexia and its various descriptions and (2) assessment and screening methods and (3) the specified patient population. The search terms used for the MEDLINE (OVID) search have been included in Appendix 8.

Preliminary searches on Cochrane and DARE were conducted to check for recent or ongoing reviews. Some of the databases contained grey literature (e.g. CINAHL) but targeted searches for grey literature were conducted using the Open Grey and NHS Evidence websites (www.opengrey.eu/ and www.evidence.nhs.uk/, 2008 to August 2022). Manual searches of the reference lists of articles, relevant systematic reviews, and practice guidelines were used to identify any further studies that eluded the database searches.

4.3.4 Study selection

Titles and abstracts of identified studies were assessed by one reviewer with 10% of the titles and abstracts independently screened against the inclusion criteria by a second reviewer. Full texts of eligible papers were retrieved, and authors contacted for full text papers where necessary. Both reviewers screened the full texts of potentially eligible studies with a subset of 10% checked by the second reviewer, before being included in the systematic review. The degree of agreement was calculated using Kappa coefficients. The list of included studies where compared and discrepancies resolved by discussion and if necessary, a third reviewer was involved.

4.3.5 Data extraction

For each study, data were extracted by one reviewer and subsets (10%) of the abstracted data were independently reviewed by two reviewers. Where inconsistencies were discovered, they were resolved by consensus. Data captured included details of the studies (year published, author, study location, study design, sample size and healthcare setting); participant detail (index health condition); how cachexia was assessed (tools and methods); and any reference to a diagnostic criterion for cachexia. The reviewed studies were assessed for methodological quality using a modified quality assessment scale (222, 223) for quantitative studies as modified for use in a previous systematic review (224). The quality assessment scale was used to inform the analysis rather than to exclude studies and used scoring in the following areas: study design, randomisation procedures, sampling and baseline group description, objectivity in outcome measurements, adjustment for bias and completeness of follow up, (Appendix 9).

4.3.6 Data synthesis

As heterogeneity of study design was expected, a narrative synthesis of the findings was planned. The narrative synthesis involved the following stages: (1) a summary of study characteristics and cachexia assessments; (2) a review of the results tables to develop a preliminary synthesis; (3) and an exploration of the relationships

within and between studies using further tabulations, subgroup and thematic analysis (225).

4.4 Results

4.4.1 Search results

Following the database searches, a total of 14,532 search results were retrieved of which 12,653 titles and abstracts were assessed for eligibility and 12,153 were excluded. Five hundred full texts were reviewed for eligibility, Figure 3. Studies were most commonly excluded when the authors did not use a cachexia assessment or failed to describe any cachexia assessments used (n=107). Also, full-text articles were excluded if authors used nutritional assessments for malnutrition or weight loss but did not identify cachexia (n=75). When the systematic review searches were initially conducted in 2019, the inter-rater reliability at the title and abstract stage was 0.78 (95% CI, 0.68 to 0.88) and at the full text screening stage was 0.44 (95% CI, 0.16 to 0.72). These Kappa scores represented fair to moderate agreement between the reviewers and inconsistencies were resolved by consensus without the need for a third reviewer. In total, 98 studies were found to be eligible for inclusion into the narrative synthesis. The literature searches were updated in 2022, and there were 57 additional studies identified. A total of 155 studies were included in the narrative synthesis.

4.4.2 Study design and quality

All 155 studies used quantitative methods and two were reported in conference abstracts, (Table 1 - Appendix 10) (21, 46, 50, 140, 152, 226-375). There were 119 observational studies, 23 randomised controlled trials (RCTs), five phase I/II trials, three screening tool development studies, one audit, one feasibility and one pilot study. The observational study designs were mainly cohort in nature (n=60) and cross-sectional (n=54) and five were case-control studies.

Studies with a randomised controlled design had a higher study quality with most ranked as being moderate to high quality (50-95%). The observational studies

ranged in quality from very low to very high (25-100%), but most were of low to moderate quality (Table 1 - Appendix 10).

4.4.3 Participants

A total of 90,743 patients were recruited across the studies (sample sizes ranged from seven to 55,345). Most patients had cancer-related cachexia, in 129 studies, and the remaining 26 studies recruited patients with a range of chronic conditions.

4.4.4 Cachexia diagnostic criteria

Studies included in the narrative synthesis described the assessment methods used to detect cachexia. Of the 129 cancer studies - 101 used published diagnostic criteria and 54 studies used criteria or assessments not linked to a source.

Most cancer studies published pre-Fearon 2011 did not use standardised diagnostic criteria (15/19 studies). From 2011 onwards the most used criteria were Fearon (2011) in 53 studies, Figure 4. Evans et al. (2008) was cited in 19 studies and the Fearon criteria (2006) cited in three studies. Across all studies, where the diagnostic criteria were not referenced, most (26/54) used a weight loss criterion over five percent of pre-illness weight lost in the preceding months with 15 of those using the time frame of the preceding six months.

Other studies used a weight loss of five percent at baseline or since diagnosis (240, 254, 316), in the past month (289), two months (293), three months (273, 277) or three to six months (276). The second most common weight loss criterion was 10% of pre-illness weight loss measured at baseline or lost since diagnosis (233, 245, 274), or lost in the preceding three (313) or 6 months (231, 319).

All of the non-cancer studies (n=26) used diagnostic criteria. Evans et al. (2008) was used in 10 studies with the use of a disease specific criteria reported in six studies. Patients in these studies had the following chronic conditions - CHF (229, 278, 288, 304); and COPD (242, 257, 265); and RA (216, 258, 270, 310, 348). Details of the diagnostic criteria used are listed in Table 2, Appendix 11.

4.4.5 Cachexia prevalence

Forty studies used the presence of cachexia as an inclusion criterion. The mean prevalence in studies with a single prevalence calculation was 36.5% (n=103, range 0.0 - 90.3%). The mean prevalence for cancer-related cachexia was 40.6% (range fromo -90.3%) and 24.0% (range from 0.6 -57.1%) for non-cancer related cachexia. The highest cachexia prevalence (60% and above) was reported in 11 studies with patients with lung (282, 301) , gastrointestinal (287, 376), pancreatic cancers (264, 284, 292, 337), head and neck cancer (362) and multiple cancer sites (342, 343).

Body composition assessments did not affect the reported cachexia prevalence. The mean prevalence of cachexia in studies with a body composition assessment was 36.7% (70 studies) vs 36.3% (33 studies) in studies without a body composition assessment.

Additionally, studies where multiple diagnostic criteria were used reported higher prevalence rates of cachexia using Fearon (2011) (21, 46, 308, 309). Wallengren et al. assessed 405 patients with cancer and reported cachexia prevalence of 45% (Fearon 2006), 33% (Evans 2008) and 85% (Fearon 2011) (46). This was replicated by Vanhoutte et al. where cancer-related cachexia prevalence was 17.9% (Evans 2008) vs 49.7% (Fearon 2011). By contrast, Zopf et al. reported different results when they compared three diagnostic criteria used to identify cachexia in a cohort of older patients (375). Of the 100 patients in the study - 32, 26 and 24 patients were identified as cachectic by the diagnostic criteria of Evans (233), Bozzetti (233) and Fearon (9) respectively. It was interesting to note that a third of the 100 patients in the study had cancer and the three definitions identified a significantly higher proportions of oncology patients as cachectic than the non-oncological patients(375).

4.4.6 Cachexia assessments

All but one study used weight measurements to calculate either current weight or weight loss across a pre-specified time period. One study used patient self-report and a clinical history of weight loss (228). In 124 studies, BMI was used to categorise

the weight status as part of the cachexia assessment or as part of a nutritional assessment. Body composition was also assessed by one or a combination of methods in 102 studies. Thirteen studies reported the use of skin fold measurement (using callipers), 48 studies used bioimpedance analysis (BIA), 18 studies used DXA scans, 19 studies used computerised tomography [CT] scans, and two studies used magnetic resonance imaging [MRI] scans.

Body composition was reported in terms of skeletal muscle mass (SMM), lean mass (LM), fat free mass (FFM) or fat mass (FM), Table 4 - Appendix 13. These measures were used to calculate indices such as the lean mass index (LMI), the fat free mas index (FFMI) and the appendicular skeletal muscle index (ASMI) which was calculated by dividing the initial measures by the square of the patient's height. FFMI and ASMI were both used to determine the presence of sarcopenia, which was a component in most diagnostic criteria for cachexia.

Other relevant assessments were those for physical function, physical activity, muscle strength, nutritional status and quality of life (Tables 1 and 4, Appendices 10 and 13). Over half of the studies (81/155) also used laboratory investigations to test for systemic inflammation using blood biomarkers such as C-reactive protein (CRP), haemoglobin (Hb), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-a).

4.4.7 Cachexia risk assessment and pre-cachexia

A small number of studies assessed cachexia risk (4/155) and their methods were weight and height measurements (for BMI), clinical assessment of weight loss from pre-illness levels, nutritional and weight loss risk assessments, physical function and frailty assessments (245, 252, 255, 370).

Additionally, studies (18/155) assessed patients for a pre-cachexic stage. There were 16 cancer and two non-cancer studies (rheumatoid arthritis and COPD) which diagnosed patients with pre-cachexia using a number of criteria, Table 3 - Appendix 12. Seven studies used Fearon's 2011 diagnostic criteria (9), three used

Muscaritoli's 2010 criteria (10), , two referenced Blum's 2014 criteria (377), one used Bozzetti's 2009 criteria (233) and one used Schols' 2014 criteria (378). An additional study used an adapted weight loss grading system originally designed to assess prognosis in cancer patients using BMI and percentage weight loss (369). Martin et al.'s (379) system, , was used to identify pre-cachexia in cancer patients if the patient was in the 'low' grade of weight loss risk.

The study of patients with rheumatoid arthritis used the Muscaritoli (2010) (10) criteria which specifies the presence of an underlying chronic disease while a COPD-specific criteria was used in the other non-cancer study, Schols et al. 2014 (378). The prevalence of pre-cachexia in these patient cohorts were 1% and 1.6% respectively. By contrast, the prevalence of pre- cachexia in patients with cancer varied from 3.6% (thoracic cancer) (249) to 75% (colorectal cancer) (233).

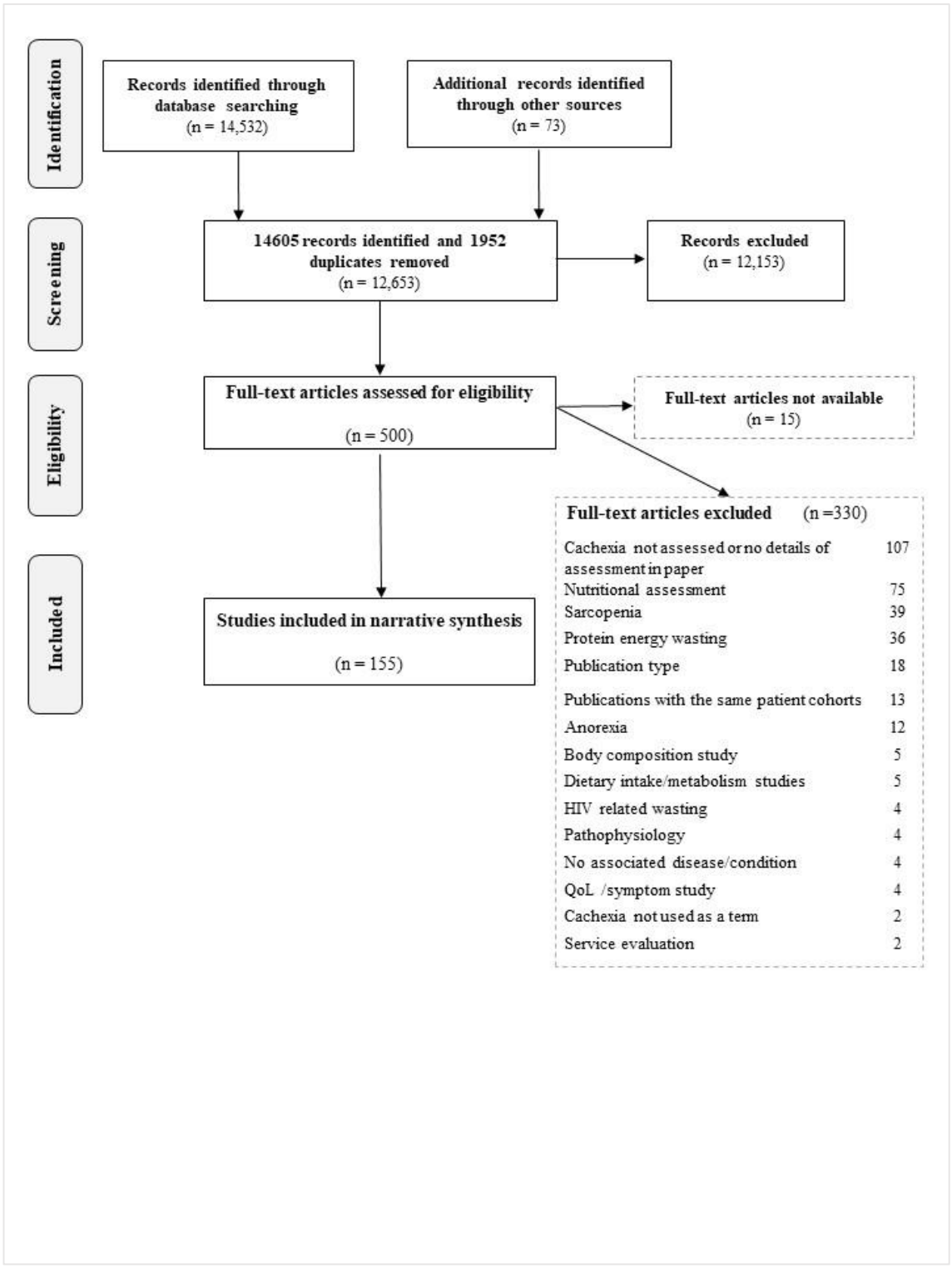
The diagnostic criteria for pre-cachexia differ in the weight loss that contributed to the diagnosis: from a weight loss of < 10% in the last 6 months (Bozzetti 2009) (233); ≤ 5% in the last 6 months (Muscaritoli 2010); or > 5% in the last 6 months (Fearon 2011). Anorexia was the most significant symptom assessed after weight loss: presence of anorexia without starvation, (Fearon 2011); anorexia or anorexia-related symptoms (Muscaritoli 2010); or anorexia in 'symptomatic' pre-cachexia or no anorexia in 'asymptomatic' pre-cachexia (Bozzetti 2009) (233).

Additionally, the studies also assessed patients for the presence of a systemic inflammatory response (Muscaritoli 2010), metabolic change (Fearon 2011) or fatigue/early satiation (Bozzetti 2009) (233). Most studies used a nutritional or quality of life questionnaire for reporting symptoms (e.g. EORTC QLQ C30 subscale or FAACT), but other systemic disturbances were ascertained through laboratory parameters (e.g. CRP and Hb), see Tables 1 and 3 in Appendices 10 and 13. There were no assessments for body composition needed for the pre-cachexia diagnostic criteria referenced in these studies.

4.4.8 Settings

Most studies were set in Europe (76 studies) and North America (26 studies). In terms of healthcare settings, all of the studies took place in secondary or tertiary care with two multi-site studies in hospital and community (hospice) sites.

Studies did not routinely describe the healthcare professionals or personnel who assessed patients for cachexia. Only 29 of the studies described teams or individuals responsible for patient assessments ranging from medical staff (18 studies), dietitians/nutritionists (16 studies), research staff (investigators, healthcare professionals or coordinators in three studies), nursing staff (three studies), and palliative care team members (one study).



Source: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2646(6): e100097.doi10.1371/journal. pmed1000097

Figure 3: PRISMA Flow diagram - a systematic review of the screening and identification of cachexia, by healthcare setting

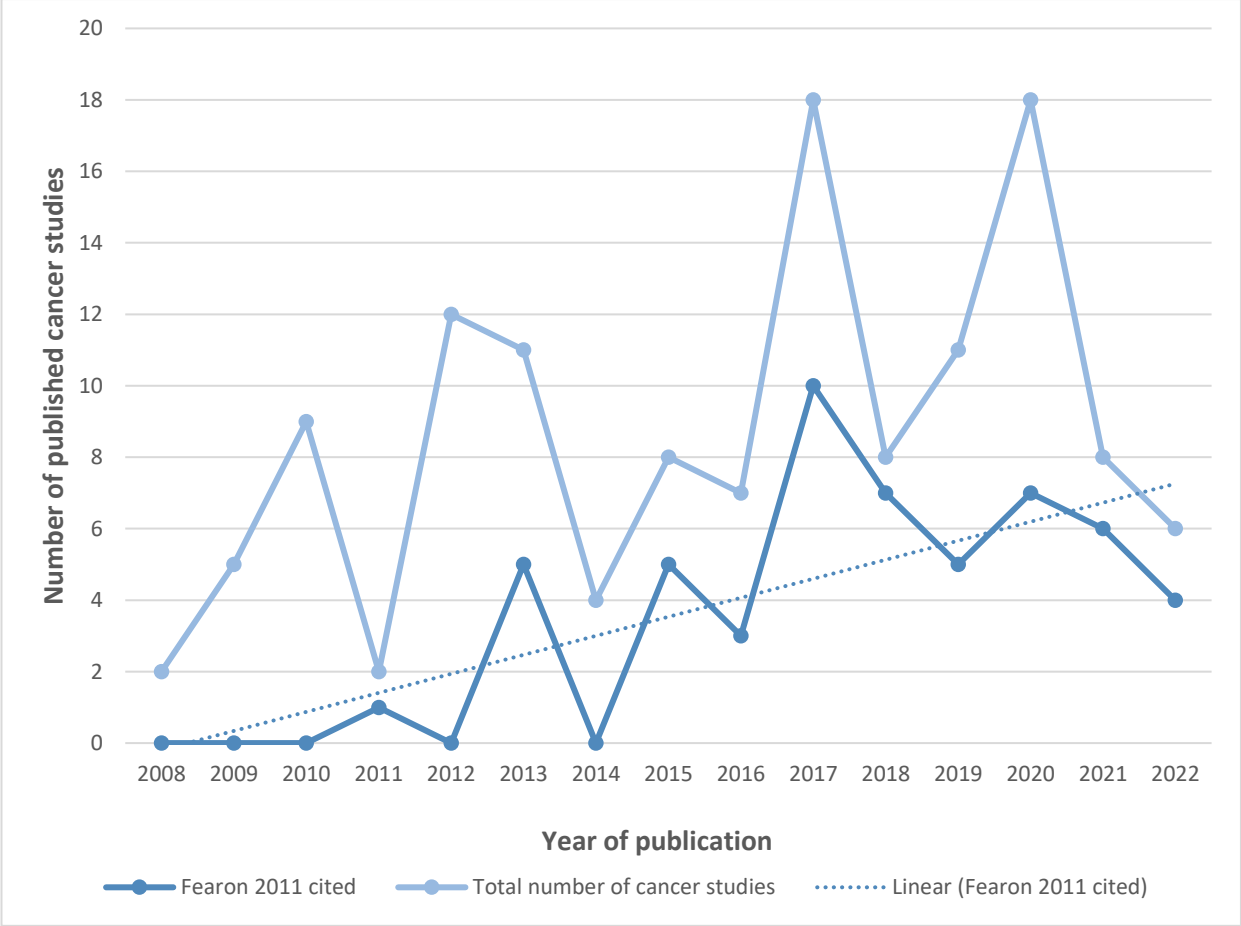


Figure 4: The number of cancer studies citing Fearon (2011)

4.5 Discussion of systematic review findings

4.5.1 Overview

Cachexia assessments were classified in five main categories: weight loss/weight status, body composition, physical function, nutritional status and inflammatory markers. All of the 155 identified studies were conducted in secondary and tertiary clinical settings and used a variety of assessments with little standardisation. Most assessments reported here are not commonly used in primary care although the 18 studies which assessed pre-cachexia and the risk of developing cachexia used methods that could be used outside of specialist settings.

Body composition was seen to be increasingly assessed by BIA, a low technology method, which accompanied by appropriate malnutrition/weight loss screening

tools or inflammatory markers could pick up early markers of cachexic weight loss in at-risk patient groups.

4.5.2 Cachexia diagnostic criteria

In journal articles published after 2011, the Fearon cachexia definition was commonly referred to and the results of the review show an increase in the use of Fearon criteria to diagnose cachexia in patients with cancer (9). Where studies did not reference a source for the criteria used, the most commonly used weight loss criterion was 5% of weight loss in the previous 6 months (26/54 studies). This was the one of three components in the Fearon criteria, and its use suggests an increasing standardisation of the weight loss associated with cachexia.

Cancer cachexia studies published before 2011, (pre-Fearon 2011) did not often refer to a published diagnostic criteria despite the existence of Evans' diagnostic criteria published in 2008 (8). This suggests that there was a lack of studies validating Evans' criteria in patient populations with cancer in the intervening years. Evans' criteria for all causes of cachexia include non-weight loss factors such as such as inflammatory markers, anorexia and fatigue. There are limitations in incorporating fatigue, anaemia and anorexia as these are also commonly encountered as part of the disease trajectory and as a consequence of treatment, especially in patients with cancer (266). Evans' criteria reflect the systemic changes found in cachexia but Fearon et al.'s criteria concentrates on changes to body weight and body composition. Fatigue and anorexia were often assessed in the included studies through the use of measures to assess symptom burden and quality of life, which reflects clinical practice in secondary or tertiary care settings, but the cachexia criteria used most (Fearon 2011) did not incorporate them.

Fearon's 2011 criteria includes the depletion in skeletal muscle mass (sarcopenia) as well as weight loss in the diagnostic framework. Loss of muscle mass in patients with cancer has been independently associated with mortality irrespective of BMI and the amount of weight lost, especially in overweight or obese patients (22, 380). The authors of the 2011 consensus definition relied on measurements of muscle

mass compared to reference levels. They suggest that this was a starting point and that studies were needed to further classify and define cachexia by examining cut-off values of BMI, weight loss and muscle mass depletion that can be linked to patient outcomes such as survival or loss of function (9). The publication of a number of dataset-based studies shows that this has started to happen (22, 379, 381, 382). This is especially important when considering changes to body composition in increasingly overweight and obese patients with cancer where weight loss might be minimal or not apparent.

Evans' criteria were used in a third of the non-cancer studies included in this narrative synthesis. This suggests a paucity of studies validating its use in patient populations with chronic diseases or conditions. Or more likely, that of all the disease groups, cachexia is more commonly recognised as occurring in cancer and this is reflected in the greater number of studies conducted.

4.5.3 Cachexia prevalence

In this review, non-cancer studies reported lower prevalence of cachexia than in the cancer studies, which has been reported elsewhere (48). It was also noted that cachexia prevalence rates differed where studies used multiple diagnostic criteria in the same patient populations. The Fearon (2011) criteria diagnosed more patients with cachexia than other criteria (21, 46, 308, 309). Although the Fearon (2011) diagnostic criteria is based on weight loss and body composition, we noted in cancer studies that cachexia prevalence was similar in studies just using weight loss as well as in those using weight loss and body composition.

4.5.4 Body measurements and assessments

The Fearon diagnostic criteria (2011) advocated that sarcopenia could be assessed using the following methods: cross-sectional imaging (CT or MRI), dual energy imaging (DXA), anthropometry (mid-arm muscle area) and BIA (by order of preference) (9). CT scans are the gold standard measurement for body composition, preferred for their accuracy and are also commonly used as part of standard clinical care in hospital settings - particularly when diagnosing and

staging cancer (285). Routine CT scans are increasingly used to report body composition changes and its association to clinical outcomes (22, 327, 383, 384). There is potential in exploiting the routine availability of CT to use it to further assess clinical outcomes and changing body composition in patients with cancer and non-cancer conditions.

This review identified an emerging use of BIA which contrasts to the specifications of the Fearon diagnostic criteria. Fearon et al. regarded BIA as only being useful for comparing groups of patients without grossly altered body composition and a review comparing the body composition of cancer patient populations exemplifies how it may be used in a research setting (385). However, as an accessible relatively low-technology assessment tool, BIA can be adopted for use in a variety of healthcare settings (287).

4.5.5 Settings

The results show that most cachexia studies were conducted in cancer specialist care settings. Community care settings (e.g. hospices) were mentioned in two multi-site studies and in one single study but as these were oncology studies, these sites could be considered secondary or tertiary care (279, 307, 357). Studies did not routinely describe the personnel needed to assess the patients. Some assumptions can be made that the more highly resourced clinical trials and larger cohort studies would have a number of personnel conducting the patient assessments, and this would not necessarily reflect routine clinical practice.

4.5.6 Risk of developing cachexia and pre-cachexia

Fearon et al.'s consensus work incorporated a pre-cachexic stage previously defined by Muscaritoli et al. (10), where clinical and biochemical signs preceded significant UWL and other manifestations of cachexia (9). Fearon et al. suggested that patients could be monitored and preventative measures or interventions for cachexia be implemented as part of clinical management of known disease. Four studies assessed for risk of developing cachexia in patients with chronic and end-stage disease and eighteen studies assessed for a pre- cachexic stage as well as

established cachexia in similar patients. All of these studies used anthropological measurements and clinically assessed weight loss from pre-illness levels of weight or in the last 6 or 12 months. The cachexia risk studies used nutritional questionnaires, amongst other tools, to assess the risk of weight loss and the development of malnutrition while the pre-cachexia studies used assessments and tools to determine the presence of anorexia or metabolic changes with levels of weight loss as determined by various diagnostic criteria. However, the cachexia risk studies investigated the risk of developing cachexia in patients newly diagnosed with cancer or in those with comorbidities attending secondary and tertiary referral centres. By this stage, it may be too late for any interventions. Similarly, the majority of studies that identified patients with pre-cachexia also assessed the whole patient cohort for cachexia and these patients were already receiving cancer treatment or had an established chronic condition. One retrospective cohort study observed cachexia or "overt pre-treatment weight loss" in 34% of patients newly diagnosed with cancer and they observed weight loss that didn't meet that threshold as "minimal weight loss" or pre-cachexia in 3.6% of patients (249).

One in five newly diagnosed patients with pancreatic cancer have already experienced "significant weight loss of over 15%" at diagnosis (386). Glare and colleagues found that referrals to a nutritional rehabilitation centre for patients with cancer tended to be at a stage when patients exhibited clinically obvious cachexia symptoms - to the frustration of the study authors who set up this service for early intervention (252). Even though these studies for detecting cachexia risk and pre-cachexia were conducted in hospital settings, the assessment methods used could also be used in non-specialist care settings either for monitoring at-risk populations or at the point of referral to secondary care.

4.5.7 Primary care

Although pre-cachexia as an early stage of cachexia is disputed by some (14), and prevalence of pre-cachexia in the included studies varied widely in this systematic review, it could present another opportunity to detect the onset of a cachectic process. This would be possible if assessments were conducted outside of the

context of known disease or, in other words, in non-secondary or tertiary care. However, this review shows that cachexia assessment remains solely in the domain of secondary or tertiary care settings. This may be partly due to many of the assessment methods in use being specialist tests that are unavailable to primary care physicians. Simple weight and height measurements are routinely undertaken in some primary care settings and inflammatory markers are regularly tested but the signatures of cachexia poorly understood. Without greater understanding of how best to assess patients at the pre-cachectic stage in primary care, significant levels of UWL will continue to be the first clinical sign that prompts a referral for further investigation in some patients (387). This also raises a question about the place of responsive preventative measures for cachexia on which the evidence is also unclear.

4.5.8 Strengths and limitations

A strength of this review is that we focused solely on assessments that lead to a diagnosis of cachexia. A number of potentially relevant studies were excluded due to the interchangeable use of the terms 'malnutrition' and 'sarcopenia' for cachexia and for concentrating on assessments of the patients' nutritional status. These studies used the same assessments for weight loss and changes to body composition but did this without reference to cachexia as a condition or without the assessments leading to a diagnosis of cachexia.

A limitation is that we excluded some studies, which could have been particularly relevant, that assessed sarcopenia and weight loss in patients with cancer. These studies were excluded, however, when they did not specifically assess for cachexia as a condition even though weight loss with sarcopenia is a diagnostic criterion for cachexia (9).

Finally, studies conducted over a number of years may have used older diagnostic criteria (or no published criteria) for their assessment of patients before the publication of the main consensus criteria in 2008 and 2011. Consequently, in cancer cachexia studies, there may be a time lag with the adoption of Fearon et al.

as these (predominantly) observational studies were conducted over a number of years before they were published.

4.6 Conclusions of systematic review

The studies in this quickly evolving research field attempt to address an unmet need in the care of patients with advanced and end-stage disease. The main consensus definitions and diagnostic criteria for the identification of cachexia (Evans et al. and Fearon et al.) have existed since 2008. While the uptake of these diagnostic criteria has been slow and, in some cases, inconsistent, there is increasing uniformity in the language used to describe cachexia, as the amount of pre-illness weight lost in a preceding timeframe.

Clinical assessments for cachexia involved recording weight over time, body composition measurements of fat or muscle mass, and laboratory parameters reflecting systemic inflammation. These assessments occurred in secondary and tertiary care settings. This represents a missed opportunity in primary care to understand which methods could be appropriately used and whether newer assessment techniques such as BIA and imaging add value to simple anthropological and blood biomarker measurement.

An exploration of the opportunities to intervene in at-risk patient populations would be the next logical step with an evaluation of how patients could be monitored as part of routine primary care contacts or at the time of referral to specialist care.

4.7 Summary

This chapter (Chapter 4) described the systematic review conducted as part of the first phase of this PhD project. Systematic searches were conducted in electronic databases for journal articles, conference abstracts and grey literature published from 2008 to 11th April 2019 with details of studies which described the tools used to assess patients with chronic and malignant disease for symptoms of cachexia. A

total of 14,605 search results were retrieved of which 12,653 titles and abstracts were assessed for eligibility and 12,153 were excluded. Five hundred full texts were reviewed for eligibility.

I extracted data from 155 eligible studies for a narrative review with the following themes - cachexia diagnostic criteria, cachexia prevalence, cachexia assessment, cachexia risk assessment and pre-cachexia, and setting (country and healthcare setting).

Most studies were in cancer cachexia (129/155), and all were conducted in secondary or tertiary care settings. Four studies assessed the risk of developing cachexia. All but one study used weight measurements to calculate either current weight or weight loss across a pre-specified time period. Body composition was assessed in 102 studies. Patients were also assessed for muscle strength, nutritional status, and inflammatory markers. Most of the studies (101/155) used published diagnostic criteria and from 2011, 53 of the 129 cancer studies used the 2011 Fearon criteria. Where a referenced criteria was not used, a weight loss of 5% or more in the past 6 months was the most common inclusion criteria (26/54 studies).

This initial study phase allowed me to assess whether there was a gap in any healthcare settings. The main conclusions were that cancer cachexia studies were increasingly adopting the Fearon (2011) diagnostic criteria but not consistently. Few studies included in the narrative review and published before August 2022, assessed cachexia risk, and none were conducted in primary care. Furthermore, an exploration of studies that assessed the risk of developing cachexia or described pre-cachexia indicated the importance of identifying early symptoms of cachexia – such as anorexia.

A summary of the main findings of the quantitative phase of this mixed methods PhD project are presented in Chapter 5.

5 Quantitative study results

5.1 Introduction

The purpose of this study phase was twofold – (1) to identify and describe patients attending an integrated care clinic for risk of frailty who may have experienced UWL and loss of appetite in the previous 12 months and (2) to review the primary healthcare records of participants to assess the degree of weight loss and if objective weight loss was assessed and investigated in primary and community health care settings.

This chapter describes the time frame, response rate, study setting, and participant sample of the screening survey administration, as outlined in the methodology chapter (Chapter 3). The first analytical stage was a descriptive analysis of the survey responses and case note review data extracts. There were further analyses to compare the characteristics of the participants with self-reported UWL and documented weight loss to those without, to assess the factors associated with self-reported UWL and documented weight loss and factors associated with a management plan in place for significant documented weight loss (≥5%).

5.2 Recruitment and study population

Data collection was conducted at the time or shortly after multidisciplinary assessment, at the Integrated Care Clinic (ICC) or in the care home. Of the 420 patients in clinic or receiving an ICC appointment in their care home, 300 consented to be PACE study participants (response rate of 71.4%). The participants also consented to their electronic primary care records being reviewed by the research team for baseline data collection, as part of the PACE study, as described in Chapter 3. There was an additional case note review to capture documented weight measurement details. The study populations and study stages are outlined in Figure 5.

The quantitative analysis research questions were answered using themes - the characteristics of patients with self-reported UWL and how they compare with patients without self-reported UWL; the characteristics of patients with documented weight loss and how they compare with patients without documented weight loss; the association between self-reported UWL and documented weight loss; and the characteristics of patients with weight loss measurements and management of UWL compared to those without.

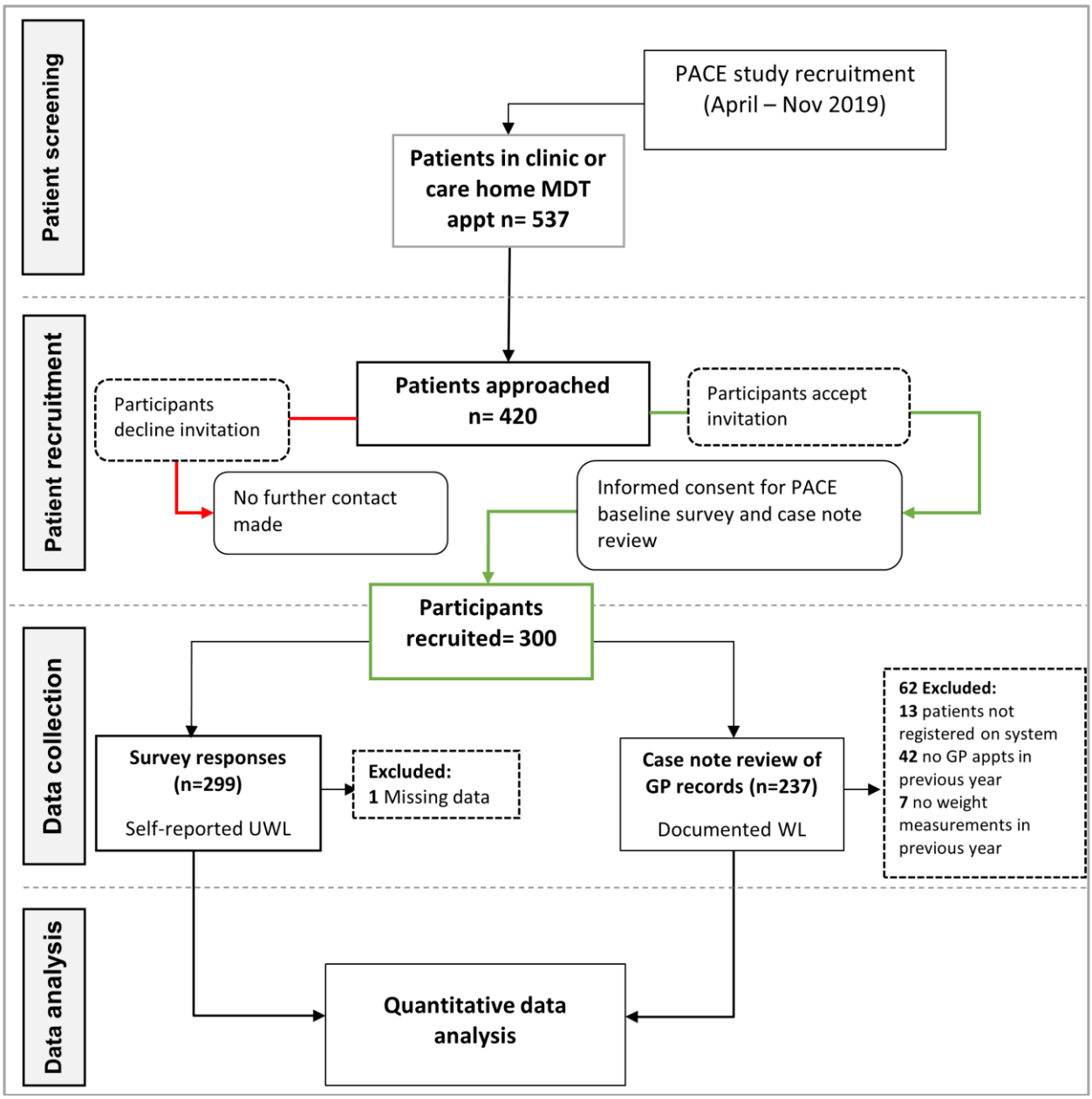


Figure 5: Patient recruitment and study populations

5.3 Theme 1 – The nature of self-reported unintentional weight loss

5.3.1 Baseline questionnaire

When asked about UWL in the past year, 74 participants (24.7%) reported having lost weight unintentionally, Table 7. When asked about changes in their diet and appetite in the past 12 months, 68.6% (n=48/70) of participants said that the amount of food they eat has decreased and a third of participants said that their appetite was 'poor' (33.8%, n=24/71). Half of the participants reported that they currently were experiencing 'poor' or 'very poor' appetite (49.3%, n=35/71). Nearly half of the participants (44.4%, n=32/72) who reported UWL thought that they had lost over a stone (>6.35 kg) in the past 12 months. When asked if they were 'worried' about their weight loss under a third said 'yes' (31.4%, n=22/70).

Table 7: Baseline questionnaire results – PACE study participants with self-reported UWL

Baseline questionnaire	Patients with self-reported UWL (n=74)	
Has how much you eat changed in the last 12 months?	**n=70**	
Yes, I eat more	6	8.6%
No, it's the same	16	22.9%
Yes, I eat less	48	68.6%
My appetite is currently:	**n=71**	
Very good	7	9.9%
Good	14	19.7%
Average	15	21.1%
Poor	24	33.8%
Very poor	11	15.5%
Currently, how does food taste to you?	**n=67**	
Very good	12	17.9%
Good	17	25.4%
Average	16	23.9%
Bad	17	25.4%
Very bad	5	7.5%
In the last 12 months, roughly how much weight do you think you have lost?	**n=72**	
A few pounds	9	12.5%
Half a stone	9	12.5%
A stone	16	22.2%

Over a stone	32	44.4%
Not sure	6	8.3%
Are you worried about your weight loss?	**n=70**	
No	45	64.3%
Yes	22	31.4%
Not sure	3	4.3%

5.3.2 Comparison of PACE study participants with and without self-reported UWL

The demographics of the study participants are reported in Table 8. Of the 299 study participants, the majority (83%) were recruited at the ICC and were mostly white (93%) and female (63%).

With respect to the risk of frailty at the time of referral to the ICC – 20% of the eFI scores were missing, 56.9% of patients were classed as having a severe risk of frailty and the rest were classed as having moderate risk (16.1%), low risk (2.3%) and no risk of frailty (1.0%). Nearly all patients had a Rockwood CFS calculated at the time of their appointment and most were categorised as mildly frail (35.3%, n =103/292), moderately frail (27.1 %, n =79/292), and severely frail (18.2%, n =53/292). The Rockwood CFS identifies patients as severely frail who are completely dependent for personal care, for whatever cause, and are not at high risk of dying in the next 6 months. More patients in a care home setting were classed as severely frail (62.3%, n=33/53) than in a private residential home setting (37.7%, n=20/53).

The living situations of the study participants, from the case note review, showed that 44.2% (n=130/294) of participants had home addresses in the most deprived quintile using the Index of Multiple Deprivation and most participants lived alone (38.9%, n=115/297) or with a spouse or partner (37.5%, n =111/297).

At the time of their ICC appointment, most of the participants (69.9%, n=200/286) were overweight (BMIs between 25 to 29.9 kg/m^2), obese (BMIs between 30 to 39.9 kg/m^2) or severely obese (BMIs > 40 kg/m^2). The mean weight of participants was

76.5 kg and mean BMI was 28.7 kg/m² - which is classified as overweight (BMIs between 25-29.9 kg/m²).

The study population was compared by whether they had self-reported UWL in the past year (24.7%, n=74/299). There were statistically significant differences in the weight and BMI at the time of appointment - 80.1 kg (SD 20.7 kg/m²) vs 65.5 kg (SD 17.1 kg/m²) (p<0.001). As might be expected, more patients who reported UWL were underweight (p<0.001) and normal weight (p=0.002). Of the patients who had not reported UWL, more were obese (39.3%) compared with those who reported UWL (16.7%), (p=0.001). There were associated statistical differences in participants affected by poor appetite in the last week. Participants with UWL in the past 12 months, were more affected by poor appetite - to a moderate (p=0.027), severe and overwhelming extent (p<0.001) than patients without UWL.

Table 8: Characteristics of PACE study participants at recruitment

Characteristic	All patients (n=299)	Patients without self-reported UWL (n=225)	Patients with self-reported UWL (n=74)	*P* value
Age (years)				
Mean (SD)	81.63 (7.6)	81.54 (7.5)	81.92 (8.0)	0.705
Sex, n (%)				
Male	108 (36.1%)	86 (38.2%)	22 (29.7%)	0.118
Female	191 (63.9%)	139 (61.8 %)	52 (70.3%)	
Ethnicity, n (%)	**n=282**			0.531
White	263 (93.3%)	197 (93.8%)	66 (91.7%)	
Mixed/multiple ethnic groups / Black African/Black Caribbean/Black British	19 (6.7%)	13 (6.2%)	6 (8.3%)	
Study setting, n (%)				0.151
Integrated care clinic	249 (83.3%)	184 (81.8%)	65 (87.8%)	
Care home	50 (13.7%)	41 (18.2%)	9 (12.2%)	
Socioeconomic deprivation, Index of Multiple Deprivation (IMD) quintiles, n (%)	**n=294**			0.454
1 (Most deprived)	130 (44.2%)	95 (43.0%)	35 (47.9%)	
2	74 (25.2%)	53 (24.0%)	21 (28.8%)	
3	46 (15.6%)	38 (17.2%)	8 (11.0%)	
4 and 5 (Least deprived)	44 (15.0%)	35 (15.8%)	9 (12.3%)	
Living situation, n (%)	**n=296**			0.266
Alone	115 (38.9%)	81 (36.3%)	34 (46.6%)	
Spouse/partner	111 (37.5%)	84 (37.7%)	27 (37.0%)	
Other family	18 (6.1%)	14 (6.3%)	4 (5.5%)	
Other	52 (17.6%)	44 (19.7%)	8 (11.0%)	
Mental capacity				0.262
Yes	245 (81.9%)	182 (80.9%)	63 (85.1%)	
No	54 (18.1%)	43 (19.1%)	11 (14.9%)	
Frailty, Rockwood Clinical Scale	**n=292**			
Score - median (IQR)	5 (5,6)	5 (5,6)	6 (5,6)	0.101
1 (Very fit) - 2 (Well)	4 (1.4%)	4 (1.8%)	0 (0.0%)	
3 (Managing well) – 4 (Vulnerable)	51 (17.5%)	42 (19.1%)	9 (12.5%)	
5 (Mildly frail	103 (35.3%)	78 (35.5%)	25 (34.7%)	
6 (Moderately frail)	79 (27.1%)	58 (26.4%)	21 (29.2%)	
7 (Severely frail)	53 (18.2%)	37 (16.8%)	16 (22.2%)	
8 (Very severely frail)	2 (0.7%)	1 (0.5%)	1 (1.4%)	
Australia-modified Karnofsky Performance Status (AKPS)				
Score - median (IQR)	60 (50,80)	60 (50,80)	60 (50,80)	0.781

Characteristic	All patients (n=299)	Patients without self-reported UWL (n=225)	Patients with self-reported UWL (n=74)	*P* value
Frailty, electronic frailty index (eFI), n (%)	**n=237**	**n=180**	**n=57**	0.369
Severe (> 0.36)	177 (56.9%)	138 (76.7%)	39 (68.4%)	
Moderate (0.25 - 0.36)	50 (16.1%)	34 (18.9%)	16 (28.1%)	
Mild (0.13. - 0.24)	7 (2.3%)	5 (2.8%)	2 (3.5%)	
No frailty (< 0.12)	3 (1.0%)	3 (1.7%)	0 (0.0%)	
Missing score	*62 (19.9%)*			
Number of comorbidities (ACE-27)				
Mean (SD)	4.34 (2.1)	4.34 (2.1)	4.35 (2.2)	0.962
Current and previous history of cancer (ACE-27)				0.635
No history	245 (81.9%)	183 (81.3%)	62 (83.8%)	
Past history and current cancer	54 (18.1%)	42 (18.7%)	12 (16.2%)	
Health-related quality of life (EQ5D 5L)	**n=295**			
EQ5D utility score - mean (SD)	0.50 (0.31)	0.51 (0.30)	0.45 (0.32)	0.117
EQ5D visual analogue score - mean (SD)	61.8 (20.2)	62.28 (19.6)	60.19 (21.8)	0.441
Weight at time of assessment	**n=296**			
Weight (kg), mean (SD)	76.49 (20.8)	80.09 (20.7)	65.51 (17.1)	<0.001*
BMI at time of assessment	**n=286**			
BMI (kg/m²), mean (SD)	28.72 (7.0)	30.10 (6.7)	24.64 (6.3)	<0.001*
Weight status at time of assessment, n (%)	**n=286**			<0.001**
Underweight (BMI < 20 kg/m²)	30 (10.5%)	10 (4.7%)	20 (27.8%)	<0.001**
Normal weight (BMI 20-24.9 kg/m²)	56 (19.6%)	33 (15.4%)	23 (31.9%)	0.002**
Overweight (BMI 25-29.9 kg/m²)	85 (29.7%)	70 (32.7%)	15 (20.8%)	
Obese (BMI 30-39.9 kg/m²)	96 (33.6%)	84 (39.3%)	12 (16.7%)	0.001**
Severely obese (BMI > 40 kg/m²)	19 (6.6%)	17 (7.9%)	2 (2.8%)	
IPOS – Poor appetite score, n (%)	**n=298**			<0.001**
Not at all	180 (60.4%)	151 (67.4%)	29 (39.2%)	<0.001**
Slightly	43 (14.4%)	32 (14.3%)	11 (14.9%)	
Moderately	48 (16.1%)	30 (13.4%)	18 (24.3%)	0.027**
Severely and overwhelmingly	27 (9.1%)	11 (4.9%)	16 (21.6%)	<0.001**

UWL - *Unintentional weight loss* / EQ5D - *EuroQol - 5D Quality of Life measure* / BMI - *Body Mass Index*
* Significant Independent T-test at the 0.05 level
** The Chi-squared statistic is significant at the 0.05 level

5.4 Theme 2 - The nature of documented weight loss

5.4.1 Documented weight loss in the 12 months before attending the ICC

Documented weight loss in the 12 months before attending the ICC was determined through reviewing the primary care health records for recorded weight measurements, Table 9. Of the 299 study participants, 249 had available records for case note review and 237 had recorded weight measurements to calculate any weight loss. Weight loss in the previous year was documented for 60% of the cohort (n = 142/237), however the weight loss ranged from 0.10 kg to 26.7 kg. Weight loss of equal to and over 5% was termed as significant and was documented for 24.5% of the participants (n = 58/237). The mean weight loss for those participants was 7.91 kg (SD 4.4) and ranged from 2.5 to 26.70 kg and the mean percentage weight loss was 10.64% (SD 5.0).

Table 9: Proportion of patients with documented weight loss in the past 12 months

Documented weight loss	
Any weight loss in previous year	**n =237**
n (%) Range (kg)	142 (59.9%) 0.10 - 26.70
Mean weight loss in previous year (kg) - mean (SD)	4.4 (4.2)
Percentage weight loss in previous year - mean % (SD)	5.70 (5.3)
Significant weight loss (≥ 5%) in previous year	**n =237**
n (%) Range (kg)	58 (24.5%) 2.50 - 26.70
Mean weight loss of ≥ 5% of weight in previous year (kg) - mean (SD)	7.91 (4.4)
Percentage weight loss in previous year - mean % (SD)	10.64 (5.0)

5.4.2 Comparison of patients with and without significant documented weight loss

When comparing the characteristics of patients with significant documented weight loss (≥ 5%) in the previous 12 months with those without significant documented weight loss, there were several differences, see Table 10. More patients recruited from the care home setting had significant documented weight loss compared with patients recruited from the ICC who mainly lived in private residential settings (22.4% vs 10.1%, p=0.017). There were differences in the living situations of the study participants with and without documented significant weight loss. For instance, participants residing in the 2nd most deprived quintile were more likely to have documented weight loss - (35.1% [n = 20/58] vs 19.4% [n = 34/179], p=0.015). Participants who lived with a spouse or partner were less likely to have significant documented weight loss (30.5% [n = 18/58] vs 45.2% [n = 84/179], p=0.046%).

Patients with significant documented weight loss were frailer (6 vs 5 on the Rockwood Clinical Scale, p <0.001) and had a poorer functional status than those without significant documented weight loss (60 vs 70, AKPS, p=0.007). These patients were also more likely to have a professional or family care giver completing the study forms due to their impaired mental capacity (20.7% vs 12.8%, p=0.144) and they had worse health related QoL scores compared to those without documented weight loss (0.43 vs 0.51, p=0.094).

Patients with significant documented weight loss in the last 12 months had a mean weight difference of 4.3 kg compared with those without significant documented weight loss (p = 0.114) and a mean difference in BMI (in the last 12 months) of 2.0 kg/m^2 (p=0.041). Patients with significant documented weight loss were also less likely to have a weight status classified as 'normal' (31.7% vs 16.8%, p=0.009), Table 10. These patients were also more affected by poor appetite in the past week to a severe and overwhelming extent when compared with those without significant documented weight loss (17.2% vs 6.7%, p=0.017).

Table 10: Comparison of patient characteristics for those with or without significant documented weight loss in the previous 12 months

Characteristic	All patients (n=237)	Patients without documented WL ≥ 5% (n=179)	Patients with documented WL ≥ 5% (n=58)	*P* value
Age (years)				
Mean (SD)	81.44 (7.6)	81.0 (7.6)	82.5 (7.5)	0.118
Sex, n (%)				0.408
Male	91 (38.4%)	70 (39.1%)	21 (36.2%)	
Female	146 (61.6%)	109 (60.9%)	37 (63.8%)	
Ethnicity, n (%)	**n=226**			0.504
White	209 (92.5%)	157 (91.8%)	52 (94.5%)	
Mixed/multiple ethnic groups / Black African/Black Caribbean/Black British	17 (7.5%)	14 (8.2%)	3 (5.5%)	
Study setting, n (%)				0.017**
Integrated care clinic	206 (86.9%)	161 (89.9%)	45 (77.6%)	
Care home	31 (13.1%)	18 (10.1%)	13 (22.4%)	
Socioeconomic deprivation, Index of Multiple Deprivation (IMD) quintiles, n (%)	**n=232**			0.047**
1 (Most deprived)	105 (45.3%)	82 (46.9%)	23 (40.4%)	
2	54 (23.3%)	34 (19.4%)	20 (35.1%)	0.015**
3	34 (14.7%)	30 (17.1%)	4 (7.0%)	
4 and 5 (Least deprived)	39 (16.8%)	29 (16.6%)	10 (17.5%)	
Living situation, n (%)	**n=235**			0.156
Alone	92 (39.1%)	82 (39.8%)	23 (44.1%)	
Spouse/partner	101 (43.0%)	84 (45.2%)	18 (30.5%)	0.046**
Other family	12 (5.1%)	9 (4.8%)	4 (6.8%)	
Other	30 (12.8%)	19 (10.2%)	11 (18.6%)	
Frailty, Rockwood Clinical Scale	**n=233**			
Score - median (IQR)	5(5,6)	5 (5,6)	6 (5,7)	0.001***
1 (Very fit) - 2 (Well)	4 (1.7%)	3 (1.7%)	1 (1.7%)	
3 (Managing well) – 4 (Vulnerable)	40 (17.2%)	36 (20.6%)	4 (6.9%)	
5 (Mildly frail	87 (37.3%)	68 (38.9%)	19 (32.8%)	
6 (Moderately frail)	62 (26.6%)	46 (26.3%)	16 (27.6%)	
7 (Severely frail)	38 (16.3%)	22 (12.6%)	16 (27.6%)	
8 (Very severely frail)	2 (0.9%)	0 (0.0%)	2 (3.4%)	

Characteristic	All patients (n=237)	Patients without documented WL ≥ 5% (n=179)	Patients with documented WL ≥ 5% (n=58)	*P* value
Australia-modified Karnofsky Performance Status (AKPS)				
Score - median (IQR)	60 (50,80)	70 (50,80)	60 (50,70)	0.007**
Electronic frailty index (eFI), n (%)				0.564
Severe (> 0.36)	143 (60.3%)	123 (75.0%)	29 (67.4%)	
Moderate (0.25 - 0.36)	45 (19.0%)	34 (20.7%)	12 (27.9%)	
Mild (0.13. - 0.24)	7 (3.0%)	5 (3.0%)	2 (4.7%)	
No frailty (< 0.12)	2 (0.8%)	2 (1.2%)	0 (0.0%)	
Missing score	*40 (16.9%)*			
Mental capacity, n (%)				0.108
Yes	202 (85.2%)	156 (87.2%)	46 (78.3%)	
No	35 (14.8%)	23 (12.8%)	12 (20.7%)	
Number of comorbidities (ACE-27)				
Mean (SD)	4.42 (2.2)	4.41 (2.2)	4.26 (2.0)	0.635
Current and previous history of cancer (ACE-27)				0.947
No history	196 (82.7%)	152 (81.3%)	49 (81.7%)	
Past history and current cancer	41 (17.3%)	35 (18.7%)	11 (18.3%)	
Health-related quality of life, EQ5D 5L	**n=236**			
EQ5D utility score - mean (SD)	0.49 (0.31)	0.51 (0.30)	0.43 (0.32)	0.094
EQ5D visual analogue score - mean (SD)	61.52 (20.1)	62.05 (20.2)	61.26 (20.1)	0.981
Mean weight loss in the previous year				
Mean weight loss (kg) - mean (SD)			7.91 (4.4)	<0.001*
Heaviest weight documented in the previous year				
Weight in kg - mean (SD)	78.23 (20.8)	79.3 (20.3)	75.0 (21.9)	0.114
Highest BMI documented in the previous year				
BMI (kg/m²) - mean (SD)	29.33 (7.0)	29.83 (6.9)	27.83 (7.4)	0.044*
Weight status, highest BMI in the previous year, n (%)				0.050
Underweight (BMI < 20 kg/m²)	20 (8.4%)	13 (7.3%)	8 (13.3%)	
Normal weight (BMI 20-24.9 kg/m²)	49 (20.7%)	30 (16.8%)	19 (31.7%)	0.009**

Characteristic	All patients (n=237)	Patients without documented WL ≥ 5% (n=179)	Patients with documented WL ≥ 5% (n=58)	*P* value
Overweight (BMI 25-29.9 kg/m²)	64 (27.0%)	51 (28.5%)	13 (21.7%)	
Obese (BMI 30-39.9 kg/m²)	85 (35.9%)	70 (39.1%)	16 (26.7%)	
Severely obese (BMI > 40 kg/m²)	19 (8.0%)	15 (8.4%)	4 (6.7%)	
IPOS – Loss of appetite score	**n=236**			0.092
Not at all	139 (58.9%)	110 (61.8%)	29 (50.0%)	
Slightly	39 (16.5%)	30 (16.9%)	9 (15.5%)	
Moderately	36 (15.3%)	26 (14.6%)	10 (17.2%)	
Severely and overwhelmingly	22 (9.3%)	12 (6.7%)	10 (17.2%)	*0.017***

* Independent samples t-test, significant at the 0.05 level
** Fisher's Exact test or Chi-squared test, significant at the 0.05 level
*** Independent Samples Mann-Whitney U Test, significant at the 0.05 level

5.4.3 Patient characteristics associated with documented weight loss

As the determination of documented weight loss in the case notes is a binomial outcome, a logistic regression model was constructed to assess the relationship between documented weight loss and the patients' demographic and clinical characteristics. Prior to this, a univariate analysis of patient characteristics (Table 11) determined which variable reached the accepted cut off for significance, as described in Chapter 3.

Twelve independent variables were identified for entry into the model. An additional sensitivity analysis excluded 'study setting' as a variable due to the number of participants recruited from care homes that had mental incapacity (44 of the 50 participants) and 'mental capacity' was another potential variable to be entered into logistic regression. Additionally, the weight-related variables were also highly correlated ('heaviest weight documented in the previous year' being used for BMI calculations and 'highest BMI documented in the previous year' being used for 'weight status'), so previous BMI and weight status as variables were excluded from the model.

The nine variables included in the logistic regression model were age, socioeconomic deprivation, living situation, frailty (Rockwood Clinical Scale), functional status (Australia-modified Karnofsky Performance Status [AKPS]), mental capacity, health-related quality of life, heaviest weight documented in the previous year and loss of appetite in the previous week (IPOS – Loss of appetite score), the baseline logistic regression model is reported in Appendix 14. The final model, Table 12, shows the variables remaining that are most highly associated with having a significant documented weight loss in the primary care records of this patient group.

Table 11: Univariate analysis of patient characteristics associated with documented weight loss in the previous 12 months

UNIVARIATE ANALYSIS - unadjusted odds ratios (OR)	**Any documented weight loss**		**Documented weight loss ≥ 5%**	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Age at ICC appointment	0.99 (0.96 - 1.03)	0.730	1.03 (0.99 - 1.07)	0.162
Sex				
Male				
Female	0.85 (0.50 - 1.43)	0.530	1.16 (0.63 - 2.13)	0.626
Socioeconomic deprivation, Index of Multiple Deprivation (IMD) quintiles				
1 (Most deprived)	ref	ref	ref	ref
2	1.95 (0.96 - 3.97)	0.065	2.10 (1.02 - 4.31)	0.044
3	0.84 (0.39 - 1.83)	0.668	0.48 (0.15 - 1.49)	0.202
4 and 5 (Least deprived)	1.08 (0.51 - 2.27)	0.843	1.23 (0.52 - 2.8)	0.636
Living situation, n (%)				
Alone	ref	ref	ref	ref
Spouse/partner	1.21 (0.53 - 2.74)	0.651	0.61 (0.31 - 1.20)	0.152
Other family	1.54 (0.68 - 3.51)	0.306	1.27 (0.36 - 4.46)	0.715
Other	0.75 (0.20 - 2.77)	0.666	1.65 (0.69 -3.92)	0.259
Frailty, Rockwood Clinical Scale	1.04 (0.84 - 1.30)	0.707	1.63 (1.22 - 2.18)	0.001
Australia-modified Karnofsky Performance Status (AKPS)	1.00 (0.98 - 1.02)	0.774	0.97 (0.95 - 0.99)	0.007
Mental capacity, n (%)				
No				
Yes	1.21 (0.59 - 2.47)	0.601	0.51 (0.24 - 1.08)	0.077
Number of comorbidities (ACE-27)	1.10 (0.97 - 1.24)	0.132	0.98 (0.85 - 1.12)	0.717*

UNIVARIATE ANALYSIS - unadjusted odds ratios (OR)	Any documented weight loss		Documented weight loss ≥ 5%	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Current and previous history of cancer (ACE-27)				
No history	ref	ref	ref	ref
Past history and current cancer	1.51 (0.77 - 2.98)	0.230	0.98 (0.46 - 2.06)	0.947
Health-related quality of life (EQ5D 5L)				
EQ5D utility score	1.12 (0.49 - 2.59)	0.777	0.43 (0.17 -1.10)	0.077
EQ5D visual analogue score	1.01 (1.00 - 1.02)	0.217	1.00 (0.98 - 1.01)	0.793
Heaviest weight in the past year (kg)	1.01 (1.00 - 1.02)	0.271	0.99 (0.97 - 1.00)	0.117
Highest BMI in the past year (kg/m²)	1.04 (1.00 - 1.08)	0.063	0.96 (0.91 - 1.00)	0.043
Weight status in the past year				
Underweight (BMI < 20 kg/m²)	ref	ref	ref	ref
Normal weight (BMI 20-24.9 kg/m²)	1.48 (0.53 - 4.15)	0.453	1.00 (0.35 - 2.85)	0.994
Overweight (BMI 25-29.9 kg/m²)	1.02 (0.38 - 2.73)	0.964	0.38 (0.13 - 1.12)	0.079
Obese (BMI 30-39.9 kg/m²)	1.52 (0.58 - 3.95)	0.396	0.36 (0.13 - 1.02)	0.054
Severely obese (BMI > 40 kg/m²)	2.12 (0.59 - 7.66)	0.251	0.41 (0.10 - 1.66)	0.209
IPOS – Loss of appetite score				
Not at all	ref	ref	ref	ref
Slightly	1.18 (0.57 - 2.44)	0.656	1.14 (0.49 - 2.66)	0.766
Moderately	1.31 (0.61 - 2.79)	0.492	1.46 (0.63 – 3.37)	0.376
Severely and overwhelmingly	1.29 (0.51 – 3.28)	0.591	3.16 (1.24 – 8.04)	0.016

**Clinically significant*

Table 12 shows the results of the logistic regression performed to ascertain the effects of the included patient characteristics on the likelihood that participants had significant documented weight loss. There were no cases that were marked as potential outliers with a standardised residual of over 2.5 standard deviations. The logistic regression model was statistically significant, $\chi^2(4) = 19.20$, p=0.001. The model explained 12.0% (Nagelkerke R^2) of the variance in documented significant weight loss and correctly classified 78.5% of cases. The Hosmer and Lemeshow goodness of fit test was not statistically significant (P=0.20) indicating that the model was not a poor fit.

The patient characteristic associated with a significant documented weight loss in the previous 12 months was frailty as measured by the Rockwood Clinical Scale. Patients with an increased frailty score (Rockwood CFS) had greater odds of having significant documented weight loss recorded in their case notes - OR 1.61 (CI 1.19 - 2.16), *p*=0.002. Additionally, patients residing in the 2nd most deprived quintile were over two times more likely to have significant documented weight loss in their case notes than those in the most deprived quintile (OR 2.20 [1.05 - 4.63], *p* =0.038).

Table 12: Patient characteristics associated with a significant documented weight loss in the previous 12 months.

	Documented weight loss ≥ 5%	
	Odds Ratio (95% CI)	***P* value**
Socioeconomic deprivation, Index of Multiple Deprivation (IMD) quintiles		
1 (Most deprived)	ref	0.057
2	2.20 (1.05 - 4.63)	0.038*
3	0.52 (0.16 - 1.66)	0.269
4 and 5 (Least deprived)	1.58 (0.65 - 3.85)	0.316
Frailty, Rockwood Clinical Scale	1.61 (1.19 - 2.16)	0.002*

**Significant at the p=0.05 level*

5.5 Theme 3 - Self-reported UWL and associations with documented weight loss

5.5.1 Self-reported UWL and associations with any documented weight loss

Forty-two patients (29.6% or 42/142) had documented weight loss in the 12 months before the ICC assessment where they correctly self-reported UWL, Table 13.

Two groups of patients incorrectly reported UWL - the proportion of those who did not report UWL but did have documented weight loss was 55.6% (100/180 patients) and 26.3% (15/57 patients) for those who self-reported UWL but did not have documented weight loss.

Table 13: McNemar chi-square test for association between the self-report of UWL and the documentation of any weight loss in the previous 12 months

		Documented UWL - any					
		Y		N		Total	
			%		*%*		*%*
Self-reported	Y	42	29.6%	15	16.0%	57	24..1%
UWL			*(42/57, 73.7%)*		*(15/57, 26.3%)*		*(100.0%)*
	N	100	70.4%	80	84.0%	180	75.9%
			(100/180, 55.6%)		*(80/180, 44.4%)*		*(100.0%)*
	Total	142	100.0%	95	100.0%	237	100.0%

A Chi-squared test showed that the proportion of patients reporting UWL significantly differed if there was a documented weight loss as measured in community healthcare settings in the past 12 months, $\chi2(1) = 5.92$, $p < 0.015$ and the Odds Ratio for self-reported UWL associated with having documented UWL was 2.24 (CI 1.16 - 4.33). However, in this case the McNemar chi-squared test is the most appropriate version of the Chi-Squared test to use as it is used for dichotomous data from matching pairs where the two groups are not independent, e.g. pre-and post-test study designs and case-control studies (388). It tests for the equality of marginal proportions so whether people with discordant responses or data (Y+N, N+Y) change from one to the other randomly or not (389). One can compare counts directly here as well as percentages. In Table 13, Y+Y = 42 and N+N = 80 but this is ignored in the McNemar test as it just considers the discordant pairs - Y+N = 100 and N+Y = 15. The results of the McNemar test determined that the difference in the proportion of those who self-reported UWL, with or without a documented weight loss, was statistically significant -McNemar's $\chi2(1) = 61.36$, $p=0.0001$ and the Odds Ratio for self-reported UWL associated with having documented UWL was 0.15 (CI 0.08 - 0.26).

The *p* value is evidence that there is an association between having documented weight loss and self-reporting UWL.

5.5.2 Self-reported UWL and associations with significant documented weight loss

Thirty-two patients (56.1% or 32/57) had significant documented weight loss (i.e., ≥5% weight loss) in the 12 months before the ICC assessment where they correctly self-reported UWL, Table 14.

The proportions of patients who incorrectly reported UWL were - 44.8% (26/58 patients) for those who did not report UWL but did have documented weight loss ≥5% and 43.9% (25/57 patients) for those who self-reported UWL but did not have documented weight loss ≥5%.

Table 14: McNemar chi-square test for association between the self-report of UWL and the documentation of significant weight loss in the previous 12 months

		Documented UWL ≥5%					
		Y		N		Total	
			%		*%*		*%*
Self-reported	Y	32	55.2%	25	14.0%	57	25.1%
UWL			*(32/57, 56.1%)*		*(25/57, 43.9%)*		*(100.0%)*
	N	26	44.8%	154	86.0%	180	74.9%
			(26/180, 14.4%)		*(154/180, 85.6%)*		*(100.0%)*
	Total	58	100.0%	179	100.0%	237	100.0%

Chi-squared tests were used to examine associations by testing whether proportions were equal in each category - e.g. there were 56.1% (32/57) of patients with documented UWL who correctly self-reported UWL while 14.4% (26/180) of patients without a documented UWL in their notes self-reported UWL at the clinic. The Chi-squared test showed a statistically significant association between a documented weight loss of 5% and above in the previous year and a self-report of UWL, $\chi 2(1) = 40.7$ $p < 0.001$. The Odds Ratio for self-reported UWL associated with having documented weight loss ≥5% was 7.6 (CI 3.89 - 14.79).

A McNemar chi-square test for association was also conducted between self-reported UWL and significant documented weight loss, Figure 6 and Table 14.

There was not a statistically significant association between a documented weight loss of 5% and above in the previous year and a self-report of UWL, McNemar's $\chi 2(1) = 0.000$, $p = 1.00$ (OR 0.96, CI 0.53 - 1.73).

In Table 14, the 2x2 table show discordant pairs (Y+N and N+Y) that are similar in value at 25 and 26 respectively, so there appears to be little or no direction of movement from moving from Yes to No or from No to Yes. As the P-value for the McNemar test statistic (see Figure 6) is greater than 0.05, the null hypothesis that there is no difference in the proportion of self-reported UWL, with or without documented weight loss ≥5%, is accepted.

Discordant entries: 26 (b) and 25 (c)

$$\chi 2 = \frac{[(b-c) - 1]^2}{(b+c)}$$

$$\chi 2 = [26-25| - 1]^2 / (26 + 25)$$

$\chi 2 = 0.000$ which equals $p = 1.00$

(as referenced by389, 390)

Figure 6: McNemar test statistic calculation

5.5.3 Patient characteristics associated with self-reported UWL in the previous 12 months

A logistic regression model was constructed to assess the relationship between self-reported UWL and the patients' demographic and clinical characteristics. The results of the univariate analyses of patient characteristics are described in Table

15. This stage determined which variable reached the accepted cut off for significance, as described in Chapter 3.

Twelve independent variables were identified for entry into the model. An additional sensitivity analysis had already excluded 'study setting' as a variable due to the number of participants recruited from care homes that had mental incapacity (44 of the 50 participants) and 'mental capacity' was another potential variable to be entered into logistic regression. As before, due to the weight-related variables being highly correlated, only 'heaviest weight documented in the previous year' was included in the model and 'highest BMI documented in the previous year' and 'weight status' were both excluded from the model.

The nine variables included in the baseline logistic regression model were age, socioeconomic deprivation, living situation, frailty (Rockwood Clinical Scale), total no of comorbidities, health-related quality of life (EQ5D utility score), heaviest weight documented in the previous year, any documented weight loss, significant documented weight loss (≥5%) and loss of appetite in the previous week (IPOS – Loss of appetite score). The baseline logistic regression model is reported in Appendix 14. The final model, in table 16, shows the variables remaining that are most highly associated with a report of UWL in the previous 12 months.

Table 15: Univariate analysis of possible factors associated with a self-report of UWL in the previous 12 months

UNIVARIATE ANALYSIS - unadjusted odds ratios	**Self-report of unintentional weight loss**	
	Odds Ratio (95% CI)	***P* value**
Age at ICC appointment	1.00 (0.97 - 1.04)	0.704*
Sex		
Male		
Female	1.46 (0.83 - 2.58)	0.188
Socioeconomic deprivation, Index of Multiple Deprivation (IMD) quintiles		
1 (Most deprived)	ref	0.461
2	1.08 (0.57 - 2.03)	0.823
3	0.57 (0.24 - 1.34)	0.200
4 and 5 (Least deprived)	0.70 (0.31 - 1.60)	0.395
Living situation, n (%)		
Alone	ref	0.277
Spouse/partner	0.77 (0.42 - 1.38)	0.376
Other family	0.68 (0.21 - 2.22)	0.523
Other	0.43 (0.19 - 1.02)	0.055
Frailty, Rockwood Clinical Scale	1.22 (0.97 - 1.55)	0.095
Australia-modified Karnofsky Performance Status (AKPS)	0.99 (0.98 - 1.01)	0.532
Mental capacity, n (%)		
No		
Yes	1.35 (0.66 - 2.78)	0.411
Number of comorbidities (ACE-27)	1.00 (0.89 - 1.13)	0.962*
Current and previous history of cancer (ACE-27)		
No history		
Past history and current cancer	0.84 (0.42 - 1.70)	0.635
Health-related quality of life (EQ5D 5L)		
EQ5D utility score	0.51 (0.22 -1.19)	0.118
EQ5D visual analogue score	1.00 (0.98 - 1.00)	0.439
Weight documented in the previous year (kg)	0.96 (0.94 - 0.98)	<0.001
BMI documented in the previous year (kg/m²)	0.89 (0.84 - 0.94)	<0.001
Documented weight loss - any		
No		
Yes	2.24 (1.16 - 4.33)	0.016

UNIVARIATE ANALYSIS - unadjusted odds ratios	Self-report of unintentional weight loss	
	Odds Ratio (95% CI)	***P* value**
Documented weight loss ≥ 5%		
No		
Yes	7.58 (3.89 - 14.79)	<0.001
Weight status, highest BMI in the previous year		
Underweight (BMI < 20 kg/m²)	ref	<0.001
Normal weight (BMI 20-24.9 kg/m²)	0.96 (0.34 - 2.72)	0.939
Overweight (BMI 25-29.9 kg/m²)	0.19 (0.06 - 0.56)	0.003
Obese (BMI 30-39.9 kg/m²)	0.13 (0.05 - 0.40)	<0.001
Severely obese (BMI > 40 kg/m²)	0.19 (0.04 - 0.85)	0.030
IPOS – Loss of appetite score		
Not at all	ref	<0.001
Slightly	1.79 (0.81 - 3.95)	0.150
Moderately	3.12 (1.54 - 6.33)	0.002
Severely and overwhelmingly	7.57 (3.19 - 17.98)	<0.001

**Clinically significant*

The Box-Tidwell procedure was used to assess the linearity of the continuous variables and with a Bonferroni correction, the 4 terms included in the procedure model did not have p values lower 0.0125 (0.05 divided by 4), (391). The assumption that all continuous independent variables were linearly related to the logit of the dependent variable was met. There were no outliers with a standardised residual of over 2.5 standard deviations. The logistic regression model was statistically significant, $\chi 2(8) = 73.02$, p <0.001 and explained 40.2% (Nagelkerke R2) of the variance in self-reported UWL and correctly classified 81.6% of cases. The Hosmer and Lemeshow goodness of fit test was not statistically significant (p=0.67) indicating that the model was not a poor fit.

As shown in Table 16, the variables possibly associated with a self-report of UWL were living situation, documented weight loss, significant documented weight loss (≥5%) and loss of appetite in the previous week. Participants with a living situation classified as 'other' were less likely to report UWL compared with those who lived alone, OR 0.13 (CI 0.03 - 0.51), p=0.003. Participants with a significant documented

weight loss (≥5%) were over 9 times more likely to report UWL than those without a significant documented weight loss - OR 9.44 (CI 4.20 - 21.25), $p<0.001$. Additionally, participants were more likely to report UWL if they experienced severe or overwhelming loss of appetite in the past week (OR 7.22 [2.21 - 23.56] $p=0.001$) when compared to those who reported no loss of appetite in the past week.

Table 16: Patient characteristics associated with a self-reported UWL in the previous 12 months

Characteristic	Patients n=222	Odds Ratio	95% CI	*P* value
Living situation, n (%)				
Alone	85	ref	ref	0.025*
Spouse/partner	96	1.03	0.46 - 2.33	0.937
Other family	12	0.70	0.13 - 3.89	0.686
Other	29	0.13	0.03 - 0.51	0.003*
Documented weight loss - any				
No	88			
Yes	134	0.95	0.93 - 0.97	<0.001*
Documented weight loss ≥ 5%				
No	167			
Yes	55	9.44	4.20 - 21.25	<0.001*
IPOS – Loss of appetite score				
Not at all	130	ref	ref	0.005*
Slightly	36	1.38	0.49 - 3.92	0.545
Moderately	34	2.98	1.51 - 7.70	0.024
Severely and overwhelmingly	22	7.22	2.21 - 23.56	0.001*

**Significant at the p=0.05 level*

5.6 Theme 4 - Weight loss measurements and management of UWL

5.6.1 Baseline questionnaire

The PACE participants who reported UWL in the past year (24.7%, n=74/299), were asked about mentioning or discussing their weight loss with others, Table 17. Of the participants who self-reported UWL, 31% (n=22/70) were concerned about their weight loss. When participants mentioned their weight loss to at least one other person - 32.3% mentioned it to their spouse, family member or friend, 23.2% mentioned it to their GP, 16.2% mentioned it to a hospital doctor and 10.1% mentioned it to a practice nurse.

Over half (63.2%, n=43/68) had been weighed by a healthcare professional, spouse, family member or friend in the past year. Approximately half of the participants had not been offered (35.4%, n=23/65) or had not asked for advice (15.4%, n=10/65) on how to gain weight. The most specific ways participants had been offered advice or help was in a recommendation in a change of diet (18.8%, n=13/69) and a referral to a dietetic service (13.0%, n=9/69).

Table 17: Baseline questionnaire results - help seeking and advice received by study participants with self-reported UWL

Survey question	Patients with self-reported UWL (n=74)	
Are you worried about your weight loss?	**n=70**	
Yes	22	31.4%
No	45	64.3%
Not sure	3	4.3%
Have you mentioned your weight loss to anyone?	**n= 69**	
No one	15	
One person or more	54	
(GP	*23*	*23.2%*
Family member or friend	*20*	*20.2%*
Hospital doctor	*16*	*16.2%*
Spouse	*12*	*12.1%*
Practice nurse	*10*	*10.1%*
Carer	*5*	*5.1%*
ICC doctor	*4*	*4.0%*
Another nurse	*3*	*3.0%*
Dietitian	*3*	*3.0%*
hypnotherapist	*1*	*1.0%*
Nursing home carer	*1*	*1.0%*
Social worker	*1*	*1.0%)*
Did any of the above weigh you?	**n=68**	
(GP, hospital doctor, practice nurse, another nurse, carer, spouse, family member or friend)		
Yes	43	63.2%
No	19	27.9%
Can't remember	1	1.5%
Not applicable	5	7.4%
Have any of the following offered you advice on how to gain weight?	**n=65**	
Hospital doctor	2	3.1%
Your GP	10	15.4%
Practice nurse	2	3.1%
Another nurse	1	1.5%
Carer	1	1.5%
Your spouse	3	4.6%
Family member or friend	3	4.6%
Can't remember	2	3.1%
Other person	8	12.3%
No advice offered	23	35.4%
Had not asked for advice	10	15.4%

Survey question	Patients with self-reported UWL (n=74)	
What advice/help were you given?	**n=69**	
Change in diet	13	18.8%
A referral to a dietitian	9	13.0%
A new prescription	1	1.4%
Can't remember	2	2.9%
Other help	11	15.9%
No help	21	30.4%
Not applicable	12	17.4%

5.6.2 Documented weight measurements in the past 12 months

The case note review showed that 244 PACE study participants had GP appointments in the past year and nearly all (n=237/244, 97.1%) had one or more weight measurements in their notes. Participants had a mean number of 2.94 (SD 3.4) weight measurements documented in the previous 12 months in their primary care records, Table 18. The mean number of weight measurements differed in patients with and without documented weight loss ≥5% - 4.62 vs 2.40, p<0.001.

Table 18: Weight measurements as recorded in primary care and community health appointments of older adults in the previous 12 months

Weight measurements in past 12 months	**Patients (n=237)**	**Patients without documented weight loss ≥5% n= 179 (75.5%)**	**Patients <u>with</u> documented weight loss ≥5% n= 58 (24.5%)**	***P* value**
Mean number per patient (SD)	2.94 (3.4)	2.40 (2.8)	4.62 (4.6)	0.001*

** Independent samples t-test, significant at the 0.05 level*

There were 690 appointments or consultations where a weight measurement was documented, Table 19. When categorised, most weight measurements (74.9%) were recorded in consultations with nursing staff - in primary care (32.0%, 221/690), community care (28.6%, 197/690) and specialist nursing care (14.3%,

99/690). In primary care consultations, weight measurements were generally taken as part of regular disease reviews - for instance respiratory, diabetic and cardiovascular reviews. Weight measurements appeared to be routinely collected in community nursing consultations and heart failure nurses recorded most of the weight measurements recorded in specialist nursing consultations.

5.6.3 Documented management of UWL in primary care records

It was noted, as part of the case note review, how many patients had a nutritional assessment and assessment of appetite, an investigation and further referral and any treatment for the documented weight loss instigated in primary care. There were a total of 119 investigations, assessments and treatments recorded in the previous 12 months in the primary care records of 237 PACE study participants, Table 20.

A composite measure was created to reflect the presence of one or more of these 'management actions' in the notes, as described in Chapter 3. The number of patients with one or more management actions was 62, Table 21. The proportion of patients with documented significant weight loss (≥5%) with a management action was 53.4% (n=31/58).

Table 19: Primary and community care appointments where weight of older patients were recorded in a 12-month period

Appointment types and healthcare professional		n (%)
Primary care nurse		221 (32.0%)
Unspecified	*66*	
Diabetes review	*56*	
Cardiovascular disease review	*31*	
Respiratory disease review	*27*	
Multiple disease review	*24*	
Monthly weight	*8*	
Vaccination	*4*	
Stroke review	*2*	
Renal disease review	*1*	
Memory clinic	*1*	
Vitamin injection	*1*	
Community nurse		197 (28.6%)
Specialist nurse		99 (14.3%)
Cardiovascular disease	*69*	
Unspecified	*14*	
Diabetes clinic	*6*	
Respiratory disease	*10*	
General practice doctor		56 (8.1%)
Unspecified	*51*	
Medication review	*2*	
Cardiovascular disease	*1*	
Dementia	*1*	
Diabetes review	*1*	
Dietetic service		46 (6.7%)
Telehealth		25 (3.6%)
Intermediate care		24 (3.5%)
Community pharmacy		8 (1.2%)
Community physio		9 (1.3%)
Community lymphoedema clinic		5 (0.7%)
Total		690

Table 20: Investigations and assessment of UWL as recorded in primary care and community health appointments of older adults in a 12-month period

Case note review	All patients (n=237)	Patients with doc WL (n=142)
Assessments of documented WL in past 12 months	**55**	**37**
Nutritional assessments, n	19	14
Assessment of appetite, n	36	23
Investigations and referrals of WL in past 12 months	**43**	**38**
Further referrals, n	29	27
Blood tests, n	8	7
Scans/ x-rays, n	5	3
Faecal Immunochemical Test	1	1
Any treatment of WL in past 12 months	**21**	**14**
Supplements / fortified diet	19	13
Amend diabetes treatment	1	0
Enteral feeding	1	1
Total	**119**	**89**

Table 21: Proportion of patients with a recorded management action (composite measure of the management of UWL) in the previous 12 months

Number of patients with one or more management actions documented in their notes	62
Proportion of patients with documented WL **and** one or more management actions in their notes	31.0% (44/142)
Proportion of patients with documented WL ≥5% **and** one or more management actions in their notes	53.4% (31/58)

**Management action is a composite measure of one or more of the following in the case notes - assessment / investigation / referral / treatment.*

5.6.4 Comparison of patients with and without a documented management action for their UWL

There were significant differences in study setting - more care home patients had a management action in their notes (29.5 vs 4.1%, $p<0.001$), Table 22. Patients who lived alone were less likely to have a management action (27.9% vs 44.33%, $p<0.004$) and were more likely to have a management action in their notes if they lived in an 'Other' living situation ($p<0.001$). (This category was used to classify, amongst others, care home settings).

Patients with management actions were frailer (Rockwood CFS, 6 vs 5, $p<0.001$) and had worse functional status scores (AKPS, 50 vs 70, $p<0.001$), had worse QOL scores (EQ5D utility score 0.43 vs 0.53, $p=0.072$ and EQ5D visual analogue scale scores - 59.55 vs 64.56, $p=0.145$).

For weight-related variables, patients with management actions weighed less than those without a management plan, having a mean weight difference of 16.83 kg ($p<0.001$) and mean BMI difference of 6.49 kg/m^2 ($p<0.001$). Patients were more likely to have a management action if they were underweight (20.5% vs 1%, $p<0.001$) and of normal weight (36.4% vs 14.3%, $p=0.003$) and less likely to have management action in their notes if they were overweight, obese (20.5% vs 44.9%, $p=0.005$) and severely obese. Patients with a management action plan for documented weight loss were more likely to have reported a loss of appetite to a severe or overwhelming extent in the previous week (22.7% vs 4.1%, $p<0.001$).

Table 22: Comparison of characteristics for patients with or without a management action for their documented weight loss in the previous 12 months

Characteristic	Patients with documented weight loss (n=142)	Patients without management actions in their notes (n=98)	Patients with management actions in their notes (n=44)	*P* value
Age (years)				
Mean (SD)	81.22 (7.8)	80.75 (7.7)	82.26 (7.9)	0.288
Sex, n (%)				0.853
Male	53 (37.3%)	36 (36.7%)	17 (38.6%)	
Female	89 (62.7%)	62 (63.3%)	27 (61.4%)	
Study setting, n (%)				<0.001**
Integrated care clinic	125 (88.0%)	94 (95.9%)	31 (70.5%)	<0.001**
Care home	17 (12.0%)	4 (4.1%)	13 (29.5%)	<0.001**
Socioeconomic deprivation, Index of Multiple Deprivation (IMD) quintiles, n (%)	**n=140**			0.503
1 (Most deprived)	60 (42.9%)	37 (38.5%)	23 (52.3%)	
2	39 (27.9%)	29 (30.2%)	10 (22.7%)	
3	18 (12.9%)	13 (13.5%)	5 (11.4%)	
4 and 5 (Least deprived)	23 (16.4%)	17 (17.7%)	6 (13.6%)	
Living situation, n (%)	**n=140**			<0.004**
Alone	55 (39.3%)	43 (44.3%)	12 (27.9%)	
Spouse/partner	64 (45.7%)	45 (46.4%)	19 (44.2%)	
Other family	5 (3.6%)	4 (4.1%)	1 (2.3%)	
Other	16 (11.4%)	5 (5.2%)	11 (25.6%)	<0.001**
Mental capacity				
Yes	123 (86.6%)	92 (93.9%)	31 (70.5%)	<0.001**
No	19 (13.4%)	6 (6.1%)	13 (29.5%)	<0.001**
Frailty, Rockwood Clinical Scale				
Score - median (IQR)	5 (5,6)	5 (5,6)	6 (5,7)	<0.001***
Australia-modified Karnofsky Performance Status (AKPS)				
Score - median (IQR)	60 (50,80)	70 (60,80)	50 (50,70)	<0.001***

Characteristic	Patients with documented weight loss (n=142)	Patients without management actions in their notes (n=98)	Patients with management actions in their notes (n=44)	*P* value
Frailty, electronic frailty index (eFI), n (%)	**n=116**			0.361
Severe (> 0.36)	84 (72.4%)	67 (76.1%)	17 (60.7%)	
Moderate (0.25 - 0.36)	28 (24.1%)	18 (20.5%)	10 (35.7%)	
Mild (0.13. - 0.24)	3 (2.6%)	2 (2.3%)	1 (3.6%)	
No frailty (< 0.12)	1 (0.9%)	1 (1.1%)	0 (0.0%)	
(Missing score	*26 (18.3% of 142)*			
Number of comorbidities (ACE-27)				
Mean (SD)	4.58 (2.1)	4.63 (2.1)	4.48 (2.1)	0.679
Current and previous history of cancer (ACE-27)				0.371
No history	113 (79.6%)	76 (77.6%)	37 (84.1%)	
Past history and current cancer	29 (20.4%)	22 (22.4%)	7 (15.9%)	
Health-related quality of life (EQ5D 5L)				
EQ5D utility score - mean (SD)	0.50 (0.30)	0.53 (0.30)	0.43 (0.30)	0.072
EQ5D visual analogue score - mean (SD)	62.99 (18.9)	64.56 (18.5)	59.55 (19.6)	0.145
Heaviest weight documented in the previous year (kg)				
Weight (kg), mean (SD)	80.07 (21.9)	85.29 (21.1)	68.46 (18.9)	<0.001*
Highest BMI documented in the previous year (kg/m²)				
BMI (kg/m²), mean (SD)	30.17 (7.5)	32.18 (6.9)	25.69 (6.9)	<0.001*
Weight measurements in past 12 months				
Mean (SD)	3.50 (4.1)	3.31 (4.7)	3.93 (2.4)	0.403
Weight status in the previous year (kg/m²)				<0.001**
Underweight (BMI < 20 kg/m²)	10 (7.0%)	1 (1.0%)	9 (20.5%)	<0.001**
Normal weight (BMI 20-24.9 kg/m²)	30 (21.1%)	14 (14.3%)	16 (36.4%)	0.003**
Overweight (BMI 25-29.9 kg/m²)	35 (24.6%)	27 (27.6%)	8 (18.2%)	
Obese (BMI 30-39.9 kg/m²)	53 (37.3%)	44 (44.9%)	9 (20.5%)	0.005**
Severely obese (BMI > 40 kg/m²)	14 (9.9%)	12 (12.2%)	2 (4.5%)	
IPOS – Loss of appetite score, n (%)	**n=141**			0.005**

Characteristic	Patients with documented weight loss (n=142)	Patients without management actions in their notes (n=98)	Patients with management actions in their notes (n=44)	*P* value
Not at all	80 (56.7%)	61 (62.9%)	19 (43.2%)	0.029**
Slightly	24 (17.0%)	16 (16.5%)	8 (18.2%)	
Moderately	23 (16.3%)	16 (16.5%)	7 (15.9%)	
Severely and overwhelmingly	14 (9.9%)	4 (4.1%)	10 (22.7%)	0.001**

'Management action' is a composite measure of one or more of the following in the case notes - assessment / investigation / referral / treatment.

** Independent samples t-test, significant at the 0.05 level*

*** Fisher's Exact test or Chi-squared test, significant at the 0.05 level*

**** Independent Samples Mann-Whitney U Test, significant at the 0.05 level*

5.7 Patient characteristics associated with a management action for documented weight loss in primary care records

A logistic regression model was constructed to assess the relationship between having a management plan documented in the case notes to address documented weight loss and the patients' demographic and clinical characteristics. The results of the univariate analyses of patient characteristics are described in Table 23. This stage determined which variable reached the accepted cut off for significance, as described in Chapter 3.

As before, 'study setting' was previously excluded as it was highly correlated with 'mental capacity' and 'living situation'. Of the three, 'living situation' provided more detail as to the domestic settings from which participants were recruited.
Due to the weight-related variables being highly correlated, only 'heaviest weight documented in the previous year' was included in the model and 'highest BMI documented in the previous year' and 'weight status' were both excluded.

There were 11 variables entered into the baseline logistic regression model - age, socioeconomic deprivation (IMD), living situation, frailty score (Rockwood CFS), functional status score (AKPS), mental capacity, number of comorbidities, EQ5D utility score, EQ5D visual analogue scale, heaviest weight documented in the previous year, and loss of appetite in the previous week (IPOS - Loss of appetite score), Appendix 14.

Table 23: Univariate analysis of patient characteristics associated with a management action for documented weight loss in primary care records

UNIVARIATE ANALYSIS - unadjusted odds ratios	Management action for documented weight loss	
	Odds Ratio (95% CI)	*P* value
Age at ICC appointment	1.03 (0.98 - 1.07)	0.286*
Sex		
Male		
Female	0.92 (0.44 - 1.92)	0.828
Study setting		
Integrated care clinic		
Care home	9.86 (2.99 - 32.46)	<0.001
Socioeconomic deprivation, Index of Multiple Deprivation (IMD) quintiles		
1 (Most deprived)	ref	0.507
2	0.56 (0.23 - 1.35)	0.193
3	0.62 (0.20 - 1.96)	0.415
4 and 5 (Least deprived)	0.57 (0.20 - 1.65)	0.298
Living situation, n (%)		
Alone	ref	0.011
Spouse/partner	1.51 (0.66 - 3.49)	0.331
Other family	0.90 (0.09 - 8.78)	0.925
Other	7.88 (2.29- 27.13)	0.001
Frailty, Rockwood Clinical Scale	1.62 (1.13 - 2.30)	0.007
Australia-modified Karnofsky Performance Status (AKPS)	0.95 (0.92 - 0.98)	0.001
Mental capacity, n (%)		
No		
Yes	6.43 (2.25 - 18.37)	0.001
Number of comorbidities (ACE-27)	0.96 (0.81 - 1.15)	0.677*
Current and previous history of cancer (ACE-27)		
No history		
Past history and current cancer	0.65 (0.26 - 1.67)	0.374
Health-related quality of life (EQ5D 5L)		
EQ5D utility score	0.35 (0.11 - 1.12)	0.074
EQ5D visual analogue score	0.99 (0.97 - 1.01)	0.146
Heaviest weight in the past year (kg)	0.95 (0.93 - 0.98)	<0.001
Highest BMI in the past year (kg/m^2)	0.85 (0.79 - 0.91)	<0.001
Weight measurements in past 12 months	1.04 (0.95 - 1.12)	0.409

UNIVARIATE ANALYSIS - unadjusted odds ratios	Management action for documented weight loss	
	Odds Ratio (95% CI)	***P* value**
Weight status, highest BMI in the previous year		
Underweight (BMI < 20 kg/m²)	ref	<0.001
Normal weight (BMI 20-24.9 kg/m²)	0.13 (0.01 - 1.13)	0.064
Overweight (BMI 25-29.9 kg/m²)	0.03 (0.04 - 0.30)	0.002
Obese (BMI 30-39.9 kg/m²)	0.02 (0.03 - 0.20)	0.001
Severely obese (BMI > 40 kg/m²)	0.02 (0.01- 0.24)	0.002
IPOS – Loss of appetite score		
Not at all	ref	0.015
Slightly	1.61 (0.60 - 4.33)	0.350
Moderately	1.41 (0.50 - 3.92)	0.517
Severely and overwhelmingly	8.03 (2.26 - 28.54)	<0.001

*Clinically significant
'Management action' is a composite measure of one or more of the following in the case notes - assessment / investigation / referral / treatment.

Using the Box-Tidwell procedure to assess the linearity of the continuous variables and with a Bonferroni correction, the terms included in the baseline model did not have p values lower 0.0045 (0.05 divided by 11), (391). The assumption that all continuous independent variables were linearly related to the logit of the dependent variable was met. There was a potential outlier with a standardised residual of over 2.5 standard deviations (2.64) that was examined and included into the model.

The final logistic regression model was statistically significant, $\chi^2(5) = 41.09$, p <0.001 and explained 35.6% (Nagelkerke R^2) of the variance in a documented management action for UWL and correctly classified 78.7% of cases. The Hosmer and Lemeshow goodness of fit test was not statistically significant (p = 0.687) indicating that the model was not a poor fit.

The results, as shown in Table 24, indicate that three variables (out of 11) that were possibly associated with a patient having a management action in their notes was functional status (AKPS), heaviest weight documented in the previous year, and

loss of appetite in the previous week (IPOS - Loss of appetite score). Those with an increased functional status measured using the AKPS, were slightly less likely to have a management action in their primary care records, (OR 0.95 [0.92 - 0.99, *p*=0.004)

Participants were also slightly less likely to have a management action in their primary care records with an increase in weight (in kg) with an Odds Ratio of 0.95 (0.93 - 0.98), *p* <0.001. Finally, participants were more likely to have a management action in their case notes they experienced severe or overwhelming loss of appetite in the past week (OR 8.52 [1.89 - 38.43], *p*=0.005) when compared to those who reported no loss of appetite in the past week.

Table 24: Patient characteristics associated with the management of documented weight loss of older patients

Characteristic	**Odds Ratio**	**95% CI**	***P* value**
Australia-modified Karnofsky Performance Status (AKPS)	0.95	0.92 - 0.99	0.004
Heaviest weight in the past year (kg)	0.95	0.93 - 0.98	<0.001
IPOS - Loss of appetite score			
Not at all	ref	ref	0.051
Slightly	1.27	0.43 - 3.76	0.672
Moderately	1.38	0.42 - 4.56	0.593
Severely and overwhelmingly	8.52	1.89 - 38.43	0.005

**Significant at the p=0.05 level*

5.8 Summary

This chapter describes the findings of the quantitative phase of this mixed methods study. As part of the PACE evaluation study, 250 patients aged 65 and over and at risk of moderate to severe frailty were recruited from a newly established Integrated Care Clinic (ICC). Forty-nine patients were also recruited from five care homes at the time of their ICC multidisciplinary assessment. The aims of this study phase were to describe the characteristics of the recruited participants with respect to self-reports of UWL (UWL) and loss of appetite in the past year; to describe the characteristics of those with documented weight loss in their case notes; and to describe the health seeking behaviour of the cohort with respect to UWL, the number of times they were weighed in a year and by whom and in which kind of healthcare appointment. Further analysis was conducted to investigate the potential factors associated with a self-report of UWL; significant weight loss (≥5%) being documented in the notes; and potential factors associated with a management action to address documented weight loss being recorded in the notes.

At the time of recruitment, about a third of participants were classed as obese with BMIs between 30 to 39.9 kg/m^2. The mean weight of participants was 76.5 kg and mean BMI was 28.7 kg/m^2. The proportion of patients who reported UWL in the past 12 months was 24.7% (74 participants). Patients who reported UWL when compared to patients who did not report UWL - weighed less (mean weight difference 14.58 kg, $p<0.001$), were significantly more likely to be underweight or normal weight. The variables significantly associated with a self-report of UWL were living situation, documented weight loss, significant documented weight loss (≥5%) and loss of appetite in the previous week. A quarter of the study participants had a documented weight loss ≥5% in the past 12 months (24%, n = 60/249). The mean percentage weight loss in this group was 10.7%. Patients who had significant documented weight loss were frailer (Rockwood Clinical Scale), when compared to patients without significant weight loss - more lived in care home settings, fewer lived with a spouse or partner, a higher proportion had BMIs in the normal weight

range (20-24.9 kg/m2) and more had experienced a loss of appetite in the past week to a severe or overwhelming extent.
The case note review showed that participants had a mean number of 2.9 weight measurements in the past year. Those with weight loss ≥5% had significantly more weight measurements (4.62) than those without (2.40). Three-quarters of the weight measurements (74.9%) were recorded in appointments with nursing staff and were generally taken as part of a regular disease review.

Management actions were counted in the notes (one or more actions in response to UWL of assessment, investigation, referral and treatment) and the proportion of patients with weight loss ≥5% with a management action was 53.4% (31/58). Factors associated with having a patient having a management action in case notes to address their weight loss was a decrease in functional status (AKPS), a decrease in body weight and a severe or overwhelming loss of appetite in the past week.

The baseline questionnaire provided data as to the health seeking behaviour of the 74 participants who reported UWL in the past year with respect to their weight loss. Just under a third (31%) were concerned about the weight loss. These participants were more likely to mention their UWL to a primary care doctor or a family member or friend. Over half (63.2%) had been weighed by a healthcare professional, spouse, family member or friend in the past year while half (50.4%) had not been offered or had not asked for advice on how to gain weight. The most commonly offered advice was a recommendation to change diet (18.8%).

Finally, the relationship between reporting UWL and having it documented in the notes was not clear cut when testing this association solely with the Chi-square and McNemar tests. However further logistic regressions did show that documented weight loss ≥5% was significantly associated with reporting UWL in the past year.

The following chapter (Chapter 6) describes the findings of the qualitative phase of this mixed methods study and the main themes developed after the analysis of the qualitative interview data.

6 Qualitative study results

6.1 Introduction

The previous chapter described the findings from the second (quantitative) phase of this PhD study, specifically the characteristics of the study population (adults aged 65 or over who were classed as at risk from moderate to severe frailty) and possible associations between reporting unintentional weight loss (UWL) in the past year and various factors. The findings of the third phase of the PhD are reported in this chapter and the main aim of this qualitative component was to use semi-structured interviews (Appendix 7) to further explore and describe the experience of losing weight unintentionally in this study population. Participants were identified and recruited from the quantitative study population for this purpose.

The qualitative study objectives were to elicit the views of those with UWL (and their caregivers) about their symptoms; their experience of how their symptoms have been assessed and managed by healthcare professionals in primary care settings; and what advice or guidance they were given about this weight loss.

6.2 Interview participants

Although a purposive sampling approach was planned, convenience sampling was used to recruit interview participants. The initial plan to recruit participants with varying levels of unintentional weight loss, and with a balance of care home residents and those residing in private residences. It was a challenge, however, to recruit to this study phase as the participants approached were often unwilling to further discuss UWL if they felt that it was resolving, if they were not concerned about the weight loss, or had been previously unaware of it (some patients only found out the extent of their weight loss at the ICC). Of the 74 participants who had reported UWL in the past 12 months, 38 were willing to be approached for a qualitative interview. Contact was made with 24 participants and 16 consented to

being interviewed. The others refused due to being unwell, being recently hospitalised and most were not concerned about their weight loss. Of the 14 that were not contacted – four potential participants died within weeks of their ICC assessment and 10 were either difficult to contact or I was made aware of them being unwell. I recruited 16 participants; however one patient withdrew from the study after recruitment, due to a deterioration in their health and another participant died before the interview could be scheduled.

I conducted 15 interviews in total with 14 participants who were ICC patients. Seven of the 14 interviews were with the participant and their caregiver at the same time. One patient and caregiver pair preferred to be interviewed separately. Also, two interview participants had family caregivers who spoke to me after the interviews informally (with consent from the patient) to add further information and context. The interviews took place between June 2019 and January 2020. All but one of the interviews took place in the participants' homes (one took place at the ICC).

6.3 Characteristics of interview participants

The characteristics of the participants recruited are shown in Table 25. It was difficult to recruit more male participants but the male to female ratio shown reflect the PACE study (ICC evaluation) population, as outlined in results Table 8.

6.4 Themes and findings

The thematic analysis of the qualitative interview data was inductive based and followed the phases as described by Braun and Clarke (197). Initial themes and codes that were developed in the early stages of the analysis can be found in Appendix 15.

Five themes were generated inductively from the thematic analysis, see Table 26: (1) Experiences and perceptions of appetite loss, (2) Knowledge, belief and

concerns about UWL, (3) Experiences and perceptions of UWL, (4) Family caregivers as witnesses and advocates, and (5) Help seeking for UWL responses from health care professionals.

Excerpts from the interviews with participant and caregivers have been included to illustrate the themes and sub-themes.

Table 25: Characteristics of interview participants

ID no.	Age	Gender	Weight status	UWL reported*	Carer present	Carer Age/ gender
36	81	F	Normal	> 1 stone	No**	
46	84	F	Overweight	> 1 stone	Partner	75 M
47	87	F	Underweight	Not sure	No	
61	73	F	Obese	> 1 stone	Husband	73 M
65	71	F	Normal	1 stone	No	
68	80	M	Normal	> 1 stone	Ex-partner	64 F
131	87	F	Underweight	> 1 stone	Son	61 M
132	66	F	Obese	Not sure	No	
178	66	M	Normal	> 1 stone	No	
190	85	F	Underweight	> 1 stone	No	
195	77	F	Obese	> 1 stone	No	
237	70	F	Severely obese	½ stone	Daughter	51F
238	77	F	Underweight	½ stone	Son	53 M
252	79	F	Obese	> 1 stone	Professional	29 F

* UWL reported at time of recruitment **Interviews recorded separately

[Underweight (BMI < 20 kg/m2) / Normal weight (BMI 20-24.9 kg/m²) / Overweight (BMI 25-29.9 kg/m²) / Obese (BMI 30-39.9 kg/m²) / Severely obese (BMI > 40 kg/m²)]

Table 26: Themes and sub-themes identified in the qualitative data analysis

Final themes	Sub-themes
Experiences and perceptions of appetite loss	Normalisation and rationalisation of appetite loss
	Causes of appetite loss
	Adaptations made to dietary habits and food preparation
Knowledge, beliefs and concerns about UWL	Current comorbidities and complex medical histories
	Impact of memory loss
	Unintentional weight loss and cancer
	Health literacy
Experiences and perceptions of unintentional weight loss	Descriptions and rationalisation of unintentional weight loss
	Perceptions of unintentional weight loss
	Loss of function and strength
	Benefits of weight loss to health state
	Experience of unintentional weight loss in overweight and obese participants
Family caregivers as witnesses and advocates	Role in meal preparation and witnessing appetite loss
	Role in seeking healthcare intervention
Help seeking for unintentional weight loss and responses from health care professional	Help-seeking for unintentional weight loss
	Systemic factors
	Healthcare professional response to weight loss
	Role of healthcare professionals

6.5 Experiences and perceptions of appetite loss

6.5.1 Normalisation and rationalisation of appetite loss

Loss of appetite was a common symptom experienced by participants and was often minimised or accepted as the norm. Loss of appetite was variously perceived as being associated with ageing, due to change in day-to-day activities such as no longer working, or due to not being as physical active. Most participants were aware of their loss of appetite and how their food intake had changed however, they had also adapted to this change in appetite over time and had rationalised their eating habits or behaviour in our conversations.

> *"Well, yeah. To me, it's normal"*
>
> [Participant 46]

> *"Oh no, it's just the way I eat has changed and portions have changed. I don't... I can't eat it if I have a plate loaded with food. I can't eat that."*
>
> [Participant 36]

Loss of appetite was also associated with significant changes in dietary intake or skipped meals and sometimes a change in food preferences, such as a "loss of my sweet tooth":

> *" I'm not a food person. I don't hate food. I only eat because I know I've got to, to keep alive. I don't eat breakfast, I don't eat lunch, and sometimes for my tea I'll just have some toast or a sandwich. I know it's wrong. I can cook myself a Sunday dinner and have two mouthfuls and I'll throw it. I'm not a food person really. Sweet stuff used to be really bad... like a chocaholic, but that's gone now."*
>
> [Participant 132]

An association was made between loss of appetite and getting older and this was often referred to directly; that the loss of appetite was to be expected and was seen as a normal part of ageing. This was especially the case if participants had witnessed this in their peers or had witnessed family members experiencing this as they got older.

> *"I don't have as much dinner as I did, but I think as you get older, everybody is, because you talk to people in here [residential home] and they always say they don't eat as much because you're not moving about, you're not at work. My portions are getting smaller but I still have a proper dinner."*
>
> [Participant 47]

> ***Participant:*** *... The pair of us, we just don't eat as much as we used to. The older you get, you don't really tend to.*
> ***Daughter:*** *Nana and Gran was the same, weren't they?*
>
> [Participant 237]

Where ageing was not referred to directly, then sometimes loss of appetite was seen as something that could happen as being part of normal life changes, such as adult children moving away or changes in routine due to retirement. This loss of appetite was also reflected in minimal effort food preparation and in different food choices. Participants also spoke of fatigue and lack of energy for food preparation being associated with getting older or with feeling unwell. Additionally, participants were facing a loss of enjoyment in their meals which was linked to their loss of appetite – *"Well, it's, I don't enjoy it sometimes. I eat so much and then I leave it."* [Participant 46]

> ***Participant:*** *I've always done because I got used to it when I had the kids at home a proper Sunday dinner, a proper dinner at dinner time et cetera, et cetera. Now, [husband] will come down.*

"Sandwich?" "Yes, I'll have a sandwich." "What are we going to have for tea?" "Don't know." "You know what's in there. I don't know what's in there anymore." "Yes, all right then." Then a bit later on he'll say, "I don't want much."

Interviewer: *Are you not hungry?*

Participant: *No. I say, "We'll just have another sandwich". He isn't either. We aren't eating like we did.*

[Participant 237]

6.5.2 Causes of appetite loss

Some participants could pinpoint what the trigger of their UWL was and when they lost their appetite. Commonly, in this study population, participants reported that the cause of UWL and loss of appetite was a long hospital stay or was associated with bereavement of a spouse or partner. This sometimes led to a temporary weight loss with the appetite eventually returning with some weight gain. In others, however, the loss of appetite would lead to a sustained weight loss with changed eating habits. With increasing duration of this weight loss, some participants expressed acceptance that there was now very little to be done to reverse this loss.

Participant: *Well, I started losing weight because I'd been looking after my husband, who was poorly. I started losing the weight and then he died and I still kept losing the weight. I used to be about 10"10'... I'm seven stone something now and I cannot put it on.*

Interviewer: *What's that kind of timescale? Is that...*

Participant: *It's six years since he died and I don't think I will now.*

[Participant 47]

Interviewer: *And then that [hospital admission] was three years ago, and you slowly gained it back, yeah, some of it back?*

Participant: *I think, and you see when I was about 12 stone, I was eating a lot more than what I eat now and I found if I eat too much, I can't eat it. Me portions have gone down and smaller. They, I mean even the chap across there, they came last night with me Yorkshire pudding, mince and that and mashed potato and it looked huge. But I ate it and left just a bit of mash.*

Interviewer: *Do you feel a bit intimidated by large portions?*

Participant: *Yeah, now I do. I didn't used to…*

[Participant 36]

6.5.3 Adaptations made to dietary habits and food preparation

Participants and their carers discussed the food that they liked to eat and their domestic arrangements for food preparation. Partners and family caregivers were often involved or in charge of food preparation. Participants who lived alone, if they did not cook for themselves, had a number of ways in which meals were prepared for or delivered to them:

Participant: *"I usually get a nice coffee then we'll come home and then we'll bring in all the shopping because I don't need a lot of shopping because now, I'm getting me meals. You've got one meal a day [from the neighbour] and I've got tomatoes and lettuce and stuff like that that I can use yoghurts, fruit, bananas, crackers. I've got all that - soup, I'm not keen on soups much, unless I make it myself.*

Interviewer: *Your main meal is from them [the neighbour]?*

Participant: *Yeah, and I pay her for that. Which I don't mind because it costs me more if I put the oven on. "*

[Participant 36]

"I get breakfast in, when me daughters aren't here. Yeah, I get me Sunday lunch delivered [right] which I pay for but it's very enjoyable."

[Participant 178]

There were examples of adaptations made to participant's diets in response to living alone and not having the energy (or the alertness) to cook or not having three meals a day due to changing appetites:

> *"I can use the microwave; I can do the odd bacon sandwich. I don't trust me oven. Because I do tend to bob off. So, I won't put a chip pan on, or anything like that. I've got me George Foreman, the microwave."*
>
> [Participant 178]

> *"Well, she did ask me, but she said do you eat your meals and I said yeah, but some nights I don't have the evening meal, [yeah?] I just have my breakfast with a sandwich at lunch time, but I am putting a bit back on."*
>
> [Participant 238]

Participants affected by loss of appetite would sometimes eat higher calorific food (such as full fat milk, cheese, dripping, fry ups) when they did eat. It was not always clear from all the participants who disclosed this if they did this instinctively or if healthcare professionals had recommended these dietary substitutions. For some, this is how they had always eaten, or they were eating food that appealed to them. Eating this way seemed to be used to address calorific deficits where other meals were missed or where they were eating smaller meals.

Participant described how a loss of appetite and loss of enjoyment lead to making minimal effort when alone and cooking for themselves. Other participants linked making less effort to no longer needing to cook regularly for family members. Participant 65 grew up in a large family (was the oldest of nine children) and raised a large family herself. She expressed relief at no longer cooking family meals and eating and cooking meals that she preferred.

"Now? I just eat rubbish. I still cook myself Sunday dinner. I do like roast beef or lamb chops and mashed potato. I make myself [yeah?]. I only eat peas, I don't eat vegetables."

[Participant 65]

Participants also mentioned how loss of appetite had affected their family meals and how family members would be concerned and comment on their inability to finish their food.

***Participant**: My son used to take me out and my other son takes me out and I could eat a three-course. Then I got, well couldn't...then after that I came out of hospital, I only have a child's [meal]. They keep saying, "Mam, why aren't you eating?" I said...*

***Interviewer:** You just don't have any appetite?*

***Participant:** I just can't get it down me. I feel sick, not sick but I said, "I'm full."*

***Interviewer:** Do you feel hungry?*

***Participant:** No, I never feel hungry.*

[Participant 131]

***Participant:** I was sat in [restaurant] and I couldn't eat a thing.*

***Interviewer:** And it would be tough to see a loved one not be able to...*

***Participant:** It is, well...she was 9 on Friday me youngest granddaughter and when we all went to [restaurant] she said, "You're not having any dinner grand dad?" so I said, "I'm not very hungry to today Xxxx", and she said, "I get like that now and again".*

[Participant 178]

6.6 Knowledge, beliefs and concerns about unintentional weight loss

6.6.1 Current comorbidities and complex medical histories

Participants were asked about their experience of attending the ICC and they would sometimes discuss their medical history in relation to their visit. More details of their comorbidities and the medication that they were taking emerged during the discussions. Participants would then interweave some of their underlying beliefs about UWL and what could be causing it into the narrative on their current illnesses and conditions.

With one participant, straightforward issues with swallowing meant that they were unable to eat:

> ***Participant:*** *I have a problem swallowing as well. [Okay] Like yesterday, it got really bad the swallowing and I didn't have any breakfast because of … it was blocking in me throat.*
> ***Interviewer:*** *Do things stick?*
> ***Participant:*** *It seems to block in me throat. [Right, okay] so I didn't erm…*
> ***Interviewer:*** *Is that anything of a certain, kind of consistency, or is it fluids as well or…?*
> ***Participant:*** *Yeah, I can't even drink sometimes cos it …just… me throat is just blocked, you know.*
>
> [Participant 195]

With other participants, their perceptions as to what was causing their UWL or loss of appetite was linked to several interlinking factors:

- The weight loss could be due to their various comorbidities;
- participants could be influenced by witnessing similar weight loss and illness in loved ones and family members;
- their expectations of losing weight and the onset of illness with getting older;

- and their ability to understand and process what a sudden weight loss could be linked to

> *"Yes, and he'd also been coughing up blood. So [hospital] was investigating this, like straight away, and even they thought that the cancer was back. But it's not. Oh, he's got prostate cancer. But you know, he's an 80-year-old man."*
>
> [Caregiver, participant 68]

> ***Interviewer:*** *There are a few things they need to sort.*
> ***Participant:*** *Yes, and my dizziness, at the moment.*
> ***Daughter:*** *...they can't do nowt about your kidneys because of your heart condition. They can't do nowt about your heart condition because of kidneys.*
> ***Participant:*** *My feet swell up with water, et cetera, my thighs swelling up, and I do sleep with them up. Doctor said, "I don't want to give you water tablets, because we know from the past it affects your kidney." So, I'm grappling with the devil and the deep blue sea.*
>
> [Participant 237]

Participants from this patient group often had a number of comorbidities that had contributed to their risk of having moderate to severe frailty. This led to participants reporting a very complex medical history that they often found difficult to keep track off in everyday life. This complexity included the number of specialty doctors they were seeing in secondary care, the impact of polypharmacy and difficulty in providing a consistent timeline of when diagnoses had been given or when acute medical events had happened.

> *"I don't know which was all this trouble I had with me cancer scare and then obviously I had an accident and then the water retention again. I collapsed and was in hospital for 10 days and lost three pints of blood orally. And had issues with me left lung.*

And I've had an ICD fitted and pacemaker. But this had all gone well, I had this surgery and never had no problem since. Although, last time I was in hospital because of this this bleeding, I got an emergency appointment which says could be up to 15 weeks to see a heart surgeon."

[Participant 178]

Interviewer: *You went straight on insulin from the hospital?*
Participant: *No, I've been on insulin since, what, when I had pneumonia. What… no… I think that was when I had some stents put in, after me heart attack. I've been put… having stents put, I think that was it. But the doctor's been lowering it because it was 22. No [it was] 24, it went down to 22. Now it's 12 … you know, so that's why… the doctor now because it just drops, my sugar level just drops.*

[Participant 195]

There was sometimes a disconnect with having such complex medical histories and the role that played in the participants being classified as having moderate to severe frailty risk. Despite the context of where the PACE study was conducted - only one participant mentioned frailty and they pushed back on the use of the word in relation to themself.

Husband: *That's been going on. I mean, when the GP referred you to Jean Bishop, it was because you were deemed, I know, it's this medical term frail, it doesn't mean you're feeble.*
Participant: *Do I strike you as a frail person?*
Husband: *It's a medical definition, isn't it…?*

[Participant 61]

Additionally, participants perceived that their complex medical history made it challenging for healthcare professionals to prioritise weight loss and loss of

appetite when they were managing other symptoms and illnesses. Some participants were also aware that the onset of weight loss and loss of appetite could be linked to a new disease or condition that needed investigation or could be due to one of the chronic conditions that they already had or the combination of drugs that they were taking.

> *"Well, they didn't really [follow up on the weight loss] … I mean the thing is, he's just got an awful lot wrong with him. And when I said anything about the weight loss or his memory, they said he was undergoing several tests at the time at [Hospital name] and things and they just sort of said, oh, well, let's get all this out the way first, but this has all taken months."*
>
> [Caregiver of participant 68]

> *"He [GP] said he's taking one thing at a time with being so many different things. If they can sort out what's wrong with my legs, it might stop them if they can ease the pain. That might, so he's trying out different ways."*
>
> [Participant 237]

6.6.2 Impact of memory loss

Memory loss was of concern to several participants and their caregivers. Where there were a number of medical conditions, participants and their carers expressed more concern about memory issues. There were participants who were having their memory loss investigated and one participant had recently received a diagnosis of Alzheimer's disease a month or so before the interview.

> *"The only thing… the biggest issue now, I think, for [patient] is his memory."*
>
> [Caregiver, Participant 68]

A loss of memory could affect many aspects of the participants' day to day lives but it could also be an issue for participants who struggled to remember when and what they had eaten. This was sometimes evident in conversation when participants could not remember the timeline of symptoms (when their weight loss or loss of appetite began) and who could not remember what they routinely ate. It was often the caregiver who would provide more detailed information when there were inconsistencies in the history. A loss of memory was mentioned as a reason why weight loss was not brought up in clinical consultations and one can imagine that this could present a problem in a GP appointment when a number of medical issues are being followed up.

> *"I've got a good appetite, I can eat whatever. Meat and potatoes, I'll eat. I can't get enough of those types of things."*
> *-This was later contradicted by the caregiver in a separate interview*
>
> [Participant 46]

> *I mean the thing was, if it wasn't... if it wasn't me coming in, [patient] wouldn't have... [mentioned the weight loss], he'd have completely forgotten about that.*
>
> [Caregiver of participant 68]

6.6.3 Unintentional weight loss and cancer

Unexplained weight loss is a red flag for cancer, and several participants in this interview cohort were aware of this. Cancer was often mentioned when asked why they would be concerned about UWL. The amount, speed and severity of weight loss was associated with suspected cancer. One participant had been treated for breast cancer and expressed concern that the cancer may have returned if she experienced weight loss now.

> *"...Yes, it does make me anxious [the cancer returning]. I just... thinking, "Well, what do I do?" I never even check my breasts, I*

don't even now because I'm thinking, oh well. I just think, "Well, I'll go for a mammogram in a year's time," but I never do it right anyway. I just thought, "I know the difference of the pains now. I know about it." You do think, "Is it bone cancer or..." but no, it isn't. [yeah] I know I haven't lost weight for a start and..."

[Participant 132]

Some participants had experienced cancer scares in the past. These cancer scares were also linked to sudden weight loss but only two participants had experienced weight loss that was being investigated for suspected cancer at the time of their interview. This was of particular concern to one participant because of the cancers for which he'd previously received treatment. When asked directly when UWL would be something to worry about, another participant reflected on her breast cancer experience:

"Yes, it would [concern me] because there would be no reason for me to lose weight just like that. You have to fight to lose weight usually, but when I had the cancer, I did lose weight."

[Participant 132]

6.6.4 Health literacy

A running thread through this theme was the knowledge participants had of their medical conditions and if they understood what the onset of symptoms, such as weight loss, meant and how this related to their current state of health. Participants were extremely knowledgeable when there was a family repository of knowledge (e.g. family members who were healthcare professionals) or where there was a family history or experience of certain conditions or diseases. Conversely, some participants, because of that family history, expressed some fatalism as to the likelihood of being diagnosed with those diseases and therefore seemed to think that there was little that they could do about it.

"It won't be smoking with me, because I don't smoke. It seems that you do see families, "Oh, she's like her mother." It's something in your genes, I believe. Could be wrong, but when your parents and everything else, I think it runs in the family. I really do."

[Participant 237]

On whom in the family was worried about him - "Mainly [daughter] cos she works, she's a clinical [job] at [hospital] in [city] so knew all the symptoms".

[Participant 178]

The interviews showed that participants would sometimes struggle to remember what medication they were taking and why they were taking them. Health literacy affected how participants were able to monitor their conditions and seek healthcare advice when needed. It also affected their dietary intake and what they perceived to be a healthy diet. When something like UWL occurs, poor health literacy may lead to a lack of understanding (and lack of concern) as to what this might mean to their current health state and if this might be something that they need to escalate to health care professionals. Where participants were not overly concerned about their weight loss, they were not sure what they needed from healthcare professionals so not sure what to ask from them or how their weight loss could be addressed. Some participants mentioned the use of protein drinks that had been recommended from their GP, practice nurse or family member. Participants were not consistent in how they used the drinks often citing a dislike for the way they tasted as to why they had discontinued them. It was clear in a few participants that they did not fully understand the importance of consistent use of dietary supplementation. Additionally, they did not return to their GP to ask about alternatives if they could not tolerate what was prescribed or recommended.

Interviewer: *But that was something that your GP thought would help, did you go back and say is there anything else I can drink cos I don't like it?*

Participant*: No, I don't take 'em anymore. I do like a cup of milk.*

Interviewer: *So, it's just literally because sometimes people don't like the flavour or they don't like the consistency and they and you were just…*

Participant: *No, I just like an ordinary cup of milk.*

[Participant 46]

6.7 Experiences and perceptions of unintentional weight loss

6.7.1 Descriptions and rationalisation of unintentional weight loss

Participants narrated their UWL experiences by describing their starting weight and the amount lost; by describing the speed of the weight loss; or by describing how they appeared to others when they had lost weight.

Participant: *Well, I was 13 stone, then I went down to 11. I just… I, I don't know. I just started losing weight for no reason whatsoever.*

Interviewer: *And at that time, you're eating habits were pretty the same as they are now. It's just that…*

Participant: *I just started losing weight for no reason whatsoever.*

[Participant 46]

Participant*: plus, my stomach… my legs are stopping, and my arms are stopping really thin and my face, my neck's gone all scraggy but stomach's getting massive.*

Interviewer*: Okay. So, you had a change in shape.*

Participant*: Yeah completely.*

***Interviewer**: Yeah, so is that concerning to you…just the way in things are fitting?*

***Participant**: Oh yeah, lots of my stuff I've given away, bags of it.*

***Interviewer**: It's really been impactful.*

***Participant**: Yeah, and now I'm on a 10 to a 12 before I was in, like 16 to 18.*

[Participant 65]

As with loss of appetite, weight loss was rationalised by participants in a number of ways – for instance, that it naturally accompanied appetite loss associated with getting older - *"The pair of us, we just don't eat as much as we used to. The older you get, you don't really tend to."* [Participant 237]. What was noticeable was that the rationalisation of the significance of UWL was sometimes linked to the reaction of health care professionals (also in chapter section 6.9).

"I think it is age related but I don't think that if there was anything to do, I would do it. But nobody… the doctor …and I'd just been to [hospital] for like a yearly check-up, and he's discharged me [mmm] and he never even… He just says to me, "you are underweight, but it's better than being overweight." They don't seem bothered about my weight…"

[Participant 47]

Again, as with loss of appetite, participants were able to link periods of weight loss with triggers such as a hospital stay, a prolonged period of illness and a life event such as bereavement where they had an associated loss of appetite. Where the weight loss was prolonged and had not been reversed, participants expressed some frustration of this situation but were mainly accepting of this new weight status.

"I lost such a lot of weight when… I was… when I was in the hospital and then they sent me out of hospital when I'd be there

for so long. They sent me to one of these care homes for six weeks and I lost an awful lot of weight. I got to 6 stone 12. And they said, try and eat more."

[Participant 190]

Perhaps because of this minimisation, adaptation and acceptance, not many participants expressed concern about their UWL in the interviews. They had either stopped worrying about it (even if they had discussed it with health care professionals) or were unconcerned so had not mentioned it to their GP at all. Additionally, as reported previously, participants would seek help for UWL that was sudden or rapid with no change in appetite or no apparent reason. If the UWL they experienced was not like this, then they would rationalise that it was not serious or needing to be brought to the attention of healthcare professionals (see chapter section 6.9).

Participant: *No, not really. I was losing weight and I couldn't put weight [on], and I still can't put weight on. No matter what I eat, I cannot put weight on. I don't worry about it now. I won't say I'm a worrier, I'm not, but I just think about it - "I wish I could put some weight on."*

[Participant 47]

6.7.2 Perceptions of unintentional weight loss

Participants and their caregivers spoke of the impact of weight loss on the participant's appearance. Weight loss, especially when a large amount of weight was lost suddenly, led to reactions from others. When the weight loss was marked not only did others (colleagues, friends and family members) remark on it, they often expressed shock.

Participant*: Yeah, even one of the consultants, the renal consultant, she came walking down. Dr. Xxxx and she went to*

me "Oh my God, you've really lost weight!" And one of the girls, the other nurses went "it's because she's been poorly Dr Xxxx"

[Participant 65]

"Yeah, he looked that ill and his daughter, his youngest daughter lives up [city] way, and I sent her a photo. And she sometimes has to come down here to work, so next time she came, she came here, and she got an absolute shock."

[Caregiver, participant 68]

In addition to reactions from others to the participants' weight loss, it was evident that participants had difficulty themselves in accepting their changed appearance. This commonly stemmed from the belief that they now looked their age or older as being overweight was associated with a more youthful appearance - "*Fat, it hides the wrinkles"* (Participant 47). For some participants, the change to their appearance was deeply impactful and seemed to outweigh how it might be affecting their health and wellbeing.

"No, I hate it [on being thinner]. I feel the back pain more and then I hate...looking in the mirror and I think "Who's that scrawny scarecrow?" Yeah, you know, I am not me when I look at myself now and it's happened all of a sudden. Well, that's what it feels like. I know it happened over a long time, but I hate it. I hate being thin like this."

[Participant 65]

"No, I don't think of it as an illness. I think of it from the vanity point of view, because I think I look awful. Scraggy. I daren't wear anything with short sleeves for my arms, I daren't wear a skirt because my legs are that horrible thin."

[Participant 47]

6.7.3 Loss of function and strength

Participants were particularly affected by loss of function and strength, and this was variously attributed to getting older, having chronic conditions and occasionally linked to muscle wasting and weight loss. They expressed frustration at not being able to perform everyday activities in the way that they used to when younger or before the weight loss. A number of participants particularly wanted to make use of the assessments and equipment on offer at the ICC as part of their multi-disciplinary appointments. They spoke of wanting a repeat of the physiotherapy input or additional occupational therapist assessments to help them maintain strength or improve their stamina for physical activity and aid them with performing everyday tasks.

> ***Interviewer:*** *So, in terms of strength, you've lost a little bit.*
> ***Participant:*** *I've lost quite a lot, yeah. I've lost all the muscle in my leg and muscles; I've lost muscles in my face and everything.*
> ***Interviewer:*** *So, you feel … in terms of getting up from sleeping, sitting down and to feel that that kind of stuff… is it harder?*
> ***Participant:*** *I feel it is a bit harder. Yeah, but not hard. If you know what I mean? Harder than what it was like before, it was it was effortless. Yes, you know like you just stand up like that. But now…. I think about it.*
>
> [Participant 65]

> ***Interviewer…****but in terms of your strength and in terms of your muscle tone, has any of that…*
> ***Participant:*** *It's not good.*
> ***Husband:*** *Yes, that's an area that you were hoping to perhaps get some further guidance on because I think partially because of your arthritis, you have got more feeble.*
> ***Participant:*** *Yes, I'm definitely not as strong as I was, I'm I?*
> ***Husband:*** *No, you're not as strong as you were a year ago.*

[Participant 161]

6.7.4 Benefits of weight loss to health state

Participants referred to medical conditions where they were used to having their weight discussed or monitored by health care professionals, such as Type 2 diabetes or arthritis. A number of participants were being reviewed annually by primary care nurses for their diabetes. Diet and weight loss would be discussed as part of these disease reviews. Often weight loss could make a difference to these conditions and health care professionals could previously have encouraged weight loss to alleviate pain or symptoms. One participant was being encouraged to lose weight in advance of a referral for hip surgery. UWL when it occurs, in the presence of a chronic conditions where weight loss has previously encouraged is, therefore, seen as a positive thing.

> *"For me, well I'm in remission now for me diabetes. Me diabetes is incredibly good. [Okay] You know, I'm like 5.6 [glucose reading] now and five months ago, was like 18,20, right?"*
>
> [Participant 178]

> *"They weren't concerned because also she said I'm diabetic and she said that I had... Now, what was the word? My own body was controlling my diabetes and she took me off the tablets."*
>
> [Participant 47]

6.7.5 Experience of unintentional weight loss in overweight and obese participants

The experience of UWL in overweight and obese participants was heavily influenced by their previous dietary habits or experiences of intentional weight loss. These participants had also experienced weight fluctuations in the past so were not immediately concerned by their weight loss. These participants were able

to rationalise that UWL was either part of their normal weight fluctuations or they had linked it to a life event or a specific trigger.

Some participants discussed having lifelong experiences of trying to lose weight and or had previously lost significant amounts of weight through belonging to dieting groups. Most of these participants were of the mindset that any weight loss was good. They spoke of instances where they consulted healthcare professionals in early adulthood to help them lose weight or the effect of medical treatment on their weight. Participants mentioned being prescribed slimming pills, gaining weight after being prescribed contraceptive pills as well as weight gain after a hysterectomy

> ***Interviewer:*** *You were trying to lose weight?*
> ***Participant:*** *I have been trying to lose weight for 50 years.*
>
> [Participant 131]

> ***Participant:*** *They say, "Lose weight." That's not easy to do, but I do know why I won't lose weight. They won't admit it.*
> ***Interviewer:*** *Why is that?*
> ***Participant:*** *When I was having me kids, many, many, many moons ago.... With me last two, we hadn't planned them or anything, and the doctor...put me on this pill, and that's when it started making me ... putting me weight on.*
> ***Interviewer:*** *Was it like the contraceptive pill?*
> ***Participant:*** *Yes. I had [son] and [another son] while I was still on the pill. I got to 14 stone, I think. I was only, what? 23, 24, and I said, "We've got to do something," so, they did. They did an hysterectomy in the end, and I've never lost weight since...*
> *I've never lost weight since, and I don't think I ever will no matter how much I try. I am losing weight slowly but I'll never actually lose.*
>
> [Participant 132]

One participant also mentioned that they were frustrated about the focus on weight loss when they were genetically predisposed to being overweight:

> *"This is one thing that does annoy me. People going on about losing weight. I'm roughly the same size as what me mom was before she had that colostomy done…The female side of it, we all seem to be the same. It's as if its runs in the family."*
>
> [Participant 237]

As well as long histories of trying to lose weight, there was a history of disordered eating experienced by one participant. This was disclosed after a few prompts were made around her eating habits and dietary changes that she had made. Her initial disclosure was around the difficulties in eating a vegetarian diet and how this was not catered for while in hospital (where she had lost some weight) and the challenges that she was still experiencing in eating this way. When prompted about when she originally started eating this way, she disclosed that dietary changes had begun a lot earlier:

> ***Participant:*** *I suppose so…but, I did once, what was it? You know when you stop eating and you don't want to eat?*
> ***Interviewer:*** *A fast… no?*
> ***Participant:*** *I can't think at the moment. You know when people take laxatives and that too?*
> ***Interviewer:*** *Yeah, so you were…*
> ***Participant:*** *What do you call them people?*
> ***Interviewer:*** *Er… anorexia?*
> ***Participant:*** *Yeah. I was, anorexic once. Really bad.*
> ***Interviewer:*** *Right. So that was in your… what 20s, 30s..?*
> ***Participant:*** *What started it off was…er…I started getting dizzy [Right]. I went to me doctor and he said it looked like your blood level was high. My blood pressure was high, and he said I get it down because my weight was, you know, what? [you were*

overweight?] Yes, otherwise you're going to go in the hospital. Well at that time, I had… I was bringing up two lads on my own. [Right] He's my second [referring to husband] and I was bringing two lads up on my own and I could not go into hospital and leave my kids. So, I said right I'll go on a diet. So, I stuck to the diet every bit. I stuck to the diet. He gave me a sheet, thousand calories a day and I stuck to that every day. I went down and down and down and down, and I really lost…bones sticking out. Really went down and I was dead chuffed. And so, I could get away with it. So yeah, I was dead chuffed cos I'd really lost a lot of weight.

Interviewer: *Do you think you've still got a… quite a complicated relationship with food after that?*

Participant: *Well now I don't want to put on weight. There's no way I want to put it back…weight on.*

[Participant 195]

Other participants who had previously been overweight or obese expressed some conflict about regaining weight. While they expressed regret that they had lost strength and were concerned that this impacted their ability to perform their day-to-day activities (due to fatigue), they didn't necessarily want to regain the weight. This conflict may feed into why they did not express concern about their weight loss and why they may not seek advice or help from health care professionals, see chapter section 6.9.

"I like it, I like being a bit slimmer. I'm not skinny, skinny, but I could do with putting a little bit more, but I don't want to put too much on."

[Participant 36]

6.8 Family caregivers as witnesses and advocates

6.8.1 Role in meal preparation and witnessing appetite loss

Family caregivers played a significant role in assisting their loved ones with meal preparation and encouraging them to eat.

> ***Interviewer:*** *Can you remember what you would have eaten when you were at home?*
> ***Participant:*** *Well, its slipped my mind but [partner] cooked for me. But er, I was well looked after, I'm telling ya, very well looked after.*
>
> [Participant 252]

Family caregivers were also more reliable witnesses to what the participant was eating as they would express concern if they felt that it was not enough. On occasion, they would help participants recall their levels of appetite loss and weight loss if they were prone to minimising them. For some participants, talking about food and mealtimes with their partners was fraught with tension. The interview with the participant with disordered eating, was occasionally interrupted by her partner who disagreed with what was being disclosed. When the interview was over and he showed me out of the house, he quite stridently expressed his concern about her eating habits and showed me cupboards containing food he claimed that she was not eating. Another participant also mentioned arguments that she had with her partner about her being unwell after eating.

> ***Interviewer:*** *Do actually have three meals in a day or is just the one?*
> ***Participant****: Not always [yeah, okay]. This morning…*
> ***<Husband interjects>:*** *She has cupboard full of food and she won't touch it.*
> ***Participant:*** *Xxxx, will just shut up, please? Go away…*
> ***Husband:*** *I'm speaking the truth!*
> ***Participant:*** *Will you just go away? It's nothing to do with you!*

[Participant 195]

"When we first moved in, I wasn't at all well and I kept being sick and we kept having arguments. [Husband] was saying, if you were eating enough, you wouldn't be sick. Then some days he would say, you've eaten too much, and that's why you're sick! Then it got to Christmas last year. On Boxing Day, I was in an ambulance, and we went to [hospital], and I had a poisoned appendicitis. That's why I was being sick."

[Participant 161]

6.8.2 Role in seeking healthcare intervention

Caregivers played a number of roles for the participants. One important role was in relation to health care consultations where they would often keep participants on track with appointment and interactions with health care professionals. Another driver for seeking healthcare intervention was spousal or family concern. They were pivotal in pointing out the onset of new symptoms in consultations and would often play an advocate role in healthcare consultations if they wanted health care professionals to investigate any worrying symptoms.

"We do tend to dash from medical appointment to medical appointment on some days, but that's fine.

[Caregiver of participant 161]

Interviewer: *Had they said anything about what the weight loss might be about?*
Carer: *No, not really*
Interviewer: *Okay… had they sent [patient] for any assessments for anything like that? That you can recall…?*
Carer: *Not really, have they? [no]*
Patient: *They only asked me to appointment I have now as we mentioned about me head…*

> ***Carer:*** *Well, we to Castle Hill the other day for you because you mentioned about the chest pain [yeah] and she got the all clear on that. Everything was okay there, won't it?*
> ***Patient:*** *Yeah, I had the heart things…*
> ***Carer:*** *Yeah you had, well anyhow and that's when they weighed her and er the next one she's got is with the neurologist and at the er, [Hospital name] and that's' with Dr Xxxx and think that's the 9th of July.*
>
> [Participant 46]

For some participants, tensions around loss of appetite and weight loss would spill over into healthcare appointments. This was revealed by the participant with a history of disordered eating, speaking about attending healthcare appointments with her husband:

> *" So, my problem is - he won't keep his gob shut [referring to husband]. So, I think, well what's the point? He's just going to open his gob and I just sit there, and I don't…I don't say a word. And I think well… then I come away… thinking what's the point of that because all he's done is gone shouting at them? Saying, she won't do this, she won't do that and I well…what's the point*?"
>
> [Participant 195]

6.9 Help seeking for UWL and responses from health care professionals

6.9.1 Help-seeking for unintentional weight loss

In this interview cohort, participants were generally aware that sudden onset weight loss was possibly a bad sign and a red flag to investigate for cancer. Some participants differed in how they understood their UWL and the impact to their health. Some saw the weight loss as being temporary and something from which they were already recovering. Others were used to weight fluctuations (i.e., those overweight or obese). The majority

of participants were, therefore, not concerned by the UWL that they had experienced. This meant that few sought help for their UWL.

> ***Participant:*** *I'm not bothered about it, not really. It's a good thing to lose it, I'm not saying… that… but I'm not concerned.*
>
> [Participant 252]

When pressed, participants were able to say when they would be concerned about weight loss and when they would seek medical attention. As described previously in chapter section 6.6, participants would seek medical attention for rapid weight loss that they felt could be serious. This was especially true if they had been diagnosed with cancer before or if there was family history of cancer where they had witnessed UWL in family members who went on to have cancer.

> ***Interviewer:*** *No, no. If you lost more at this stage, do you think you'd pick that up with someone?*
> ***Participant:*** *I think I would go back to doctors if I lost any more, yes.*
>
> [Participant 47]

When participants and caregivers were concerned it was often the caregiver who pushed for the patient to mention weight loss to their healthcare providers, or the caregiver would take the lead in reporting their concerns directly. The role of family caregivers is reported in chapter section 6.8. While not pushed to seek help from a family member, one participant described being encouraged to seek help by their medically trained colleagues. And as mentioned before, the reaction of others to the UWL was the impetus for participants to seek medical attention.

> *"Well, I work at [hospital] and I work on medical patients now and then and I never even noticed actually, and I knew my uniforms were getting bigger. You know, they were started to hang off me and then our matron sister, you know, got me in the*

office and said I want to have a word with you. She said, we want you to go to doctors and ask for a thyroid function test, cause we're all getting a bit worried about you, you know."

[Participant 65]

6.9.2 Systemic factors

There were several participants who expressed their frustrations on the difficulties of accessing appointments at their GP surgeries when they were asked if they had mentioned their weight loss or been weighed in a GP appointment - "*You can't always get in the doctors."* [Participant 46]. Difficulty in accessing primary care appointments was a key concern to participants who had chronic conditions. It was apparent in the interviews that participants felt they had limited time in the appointments as well as limited access to primary care appointments. Conversations around weight loss and appetite loss seemed to happen more in nursing appointments for regular disease review appointments that allowed time for weight loss to be mentioned alongside other concerns. As has been noted in chapter section 6.6, a complex medical history meant that more urgent issues may be prioritised in an appointment with a GP. It is of interest that only three interview participants went to their GP specifically for UWL. These systemic factors (appointment duration and difficulty in scheduling appointments) could be one of many contributary factors why other participants downplay weight loss or fail to mention it.

"Yeah, it was the 111 [NHS 24-hour urgent care advice and triage phone line] before. You can't get through to a doctor at the moment, can you? You ring at eight o'clock, it's engaged. And by the time you get through its half past nine. Then they say, I'm sorry, it's all booked, ring again tomorrow..."

[Participant 190]

6.9.3 Healthcare professional response to weight loss

Where participants had mentioned or discussed their weight loss there were a number of responses from healthcare professionals. Patients were able to get assessed or referred for investigations either after several appointments showed that it was an ongoing issue or when the weight loss was noticeable in its severity (suddenness and amount of weight loss) and when it was accompanied by a dramatic change in appearance. The presence of a loved one or family caregiver was also a factor as they were able to help with communicating that weight loss or loss of appetite was an ongoing issue. The persistence needed in communicating concerns was variously attributed to not having enough time in consultations, a number of medical issues already being addressed or investigated and the need to emphasis the ongoing nature of the weight loss and that it had not yet resolved.

> *"Oh heck. Yeah, we mentioned it [the UWL] on several …I mentioned it on several occasions so I know I mean, yeah, I know that [patient]'s memory is not so good so he can't remember and I now I've have mentioned it and…*
>
> [Caregiver, participant 68]

> *"They just say they know that I'm losing weight, and they just say, "Carry on. Basically, you've got your diabetes under control, so just do what you're doing."*
>
> [Participant 237]

Participant 65 had her weight loss noticed by colleagues who were healthcare professionals who then urged her to get an appointment with her GP. This resulted in immediate action and a slew of investigations on the GP seeing the very visible weight loss:

"She said, we want you to go to doctors and ask for a thyroid function test, cause we're all getting a bit worried about you, you know. So, I mean, so that's what I did and then I went to see Dr Xxxx and he said lie on the couch, and I'll examine you. When he lifted my top, he could see how much weight I'd lost, and my clothes was hanging down. Anyway, he went "oh goodness gracious!". I mean, he felt down the side of my stomach and it hurt, and he went. "Oh, I'm sending you to a hospital for x-rays"."

[Participant 65]

Interviewer: *So, you had started having a series of investigations?*

Participant: *Yeah. I had a colonoscopy, an endoscopy, a virtual colonoscopy. Erm, I had all sorts of things done, you know.*

[Participant 65]

Few participants recalled immediate or further investigations for their UWL, as only a few participants went to see their GP specifically for this issue. Other participants took their cues from their interactions with healthcare professionals who were either "not bothered" by the UWL or who were pleased that the participant had lost weight. Some participants also recalled healthcare professionals reacting positively to them being slim.

"Well, they changed my tablets a couple of times, but they never seemed bothered about my weight."

[Participant 47]

" I used to be really skinny, you know when I got married, I weighed six stone eight. When I was nine months pregnant with my oldest, I was then seven and a half stone and I was really worried about it and I always remember saying to the nurse, all

those years ago. I know I'm really thin. So, she went no we like you like this. She said it's better than some of those big tanks that come rolling in here."

[Participant 65]

6.9.4 Role of healthcare professionals

The roles of primary care staff for interview participants seemed to be giving reassurance or referring patients on to specialists for investigations or treatment. Participants used the response (or lack of response) from healthcare professionals to reassure themselves as to the significance of their UWL.

"Well, I have with the nurse, because she used to say... I mean, I used to go see the nurse regularly for my preview. Well, once a year, and I used to say to her... I knew her well with [husband], you see, and I used to say about my weight. She used to say, don't know why you're bothering and worrying about it. She said, "It'll come." But nobody's ever offered... to tell me what to do."

[Participant 47]

However, the main role of health care professionals was to refer the participants for investigations and to a specialist. The investigations mentioned were "a scan" and a specialist could be a hospital consultant though a few participants were happy to receive referrals to the dietetic service after their ICC assessment. Some participants had already received some interventions from their GP - e.g. a prescription for dietary supplementation. However, several participants discussed wanting an escalation or an external response to address their concerns about UWL, once communicated.

Interviewer: *What would you have wanted them to do had you gone to the GP? I know that this is a bit theoretical 'cos the Jean*

Bishop [ICC] appointment came up. But when you went to the GP, you were concerned, you wanted them to find out what the cause was?

***Carer**: I would have wanted them to really refer her to a hospital consultant.*

[Caregiver, participant 46]

The ICC assessment came at an opportune time for some the interview participants as they organised referrals and investigations to address weight loss and related symptoms. It also functioned as an external response that their GP was instigating. Of interest, one participant had been referred by their community pharmacist and another by their vascular surgeon. The majority were referred by their GP surgery.

While discussing their UWL, most of the participants were more concerned with addressing the resulting effects of muscle weakness and loss of function, see chapter section 6.7. Participants spoke of wanting more input from physiotherapists and occupational therapists after their initial ICC assessment. Some of the practical solutions they had received through the ICC was evident in their homes and they wanted further input and follow up to improve their strength and their ability to perform everyday activities. This could be that they thought that the referrals and interventions resulted from their referral to the ICC and were not things they would have normally received.

"I also saw the physiotherapist because my legs are so weak because I've got not just a vascular disease, but I water retention because I had a cancer scare earlier in the year [Right, okay]. I'm on water tablets continuously now. Just no strength in me legs. Just need a bit of physio really. "

[Participant 178]

***Participant:** I think it was more than that because then I had to see the person that gave me the…*

Interviewer: *Oh, the physio.*

Participant: *Yes, he gave me that <points to four-wheeled walker> and then I had somebody come and put in my handrail cable.*

Interviewer: *Oh, right, so someone came to the house?*

Participant: *Yes, to do that, and also a step to step into my shower...*

Interviewer: *Nice.*

Participant: *...and a seat.*

[Participant 36]

By contrast, a number of interview participants had already been referred to dietitians and had been prescribed or recommended dietary supplementation through their GP.

When they mentioned wanting a referral to the dietetic service, I followed up to ask what they would like the dietitians to do. Some were unsure and others said they would try to eat different types of food if suggested. One participant had started to regain weight with the help of a dietitian – they had advice to eat snacks as well as their meals. They adopted this change in diet but were still concerned with regaining strength to perform everyday household chores. Another participant was a little dismissive of the dietitian input they had already received.

Interviewer: *... If the dietitian told you to try and eat different types of food, is that something you'd try to do?*

Participant: *Yes. She just said, "Eat a bit more butter." She didn't really. "Eat a biscuit. Eat in between meals."*

[Participant 131]

6.10 Reflexive statement

This qualitative study explored the views and experiences of older patients and caregivers in their own homes in a northern English city often known for its areas of deprivation. I am a Black British, African-origin, middle-aged woman with an applied health research background. I was very much in the position of an 'outsider' to the participants who were all white British and all but one from working class backgrounds. I was invited into participants' homes relatively easily as participants had often met me previously at the Integrated Care Clinic where they were recruited for the PACE study. I reminded the participants that they had seen me or a colleague at the clinic when I phoned them to invite them to take part in the qualitative interviews. When the interviews started, however, I had to remind them and make clear that I was based in the clinic as a researcher and that my normal base was at the university. I told them that I was there to collect information about their medical history and health experiences and if this included their impressions of the clinic then they could feel free to give me honest feedback.

Some people asked me about the study, how we were evaluating the service and I was asked about my doctoral studies. Others still discussed the clinic with me as if I was part of the service and asked if I could help them with follow up visits at the clinic or they asked when they would hear back from the services or clinics to which they had been referred. I helped with information where I could but was able to feedback to the ICC. The research team had put in place a feedback process precisely for this reason.

There were times when I had to overcome some biases and preconceived notions. The Integrated Care Clinic was set up to provide a multi-disciplinary assessment for people at risk of severe frailty. The waiting rooms were not full of people who looked 'frail'. I had to overcome the notions that the risk of frailty equalled current frailty and that there was a certain look that a person with severe frailty had (i.e., underweight with noticeable physical weaknesses). The Oxford English Dictionary defines frailty as *"the condition of being weak and delicate [...]"* (392) and this is a pervading preconception for lay people. The conceptualisation of frailty have

variously classified it as a clinical syndrome, a health state or a risk state (121, 393). These preconceptions were important to overcome as when we started recruiting at the clinic, I thought there were not enough participants for me to recruit to the qualitative interviews. I needed the reminder that with increasing levels of overweight and obesity in the general population that this patient group would reflect that trend. Frailty as a condition also pertains to those who are overweight and obese and who look physically more robust than the traditional notions of frailty. The same is also true for anorexia and UWL.

There were times during the interviews when I was able to engage more with participants. Although, I do not feel I ever moved to a position of an 'insider', those moments helped with building rapport. I was asking about intentional and UWL, dietary habits and their perceptions of weight loss. As an obese woman with visible weight issues, I feel those who were also overweight or obese were able to be open and honest with me with respect to their dietary histories and experiences. Also, when some participants found out about my background and that I grew up in Yorkshire, it helped me further engage with them. I have witnessed a close family member live many years with cachexia and loss of appetite associated with chronic heart failure. When I mentioned this, I used the term 'muscle wasting'. I recall feeling anxious around family mealtimes when they were unable to eat with enjoyment and needed to be given much smaller portions. On occasion I would refer to this and I was able to demonstrate, mainly to family caregivers, that I understood what they were experiencing and or their concerns. I was aware, however, that disclosure of personal experiences needs to done sparingly as it can interfere with an interviewer's neutral objective stance and it can be a challenge to maintain the required 'empathic distance' that a qualitative researcher needs to have (394).

Family caregivers played an important role in my research, especially with respect to the qualitative interviews. As previously described in Chapter 3, patients were approached first about the study at the time of their ICC appointment by clinical staff who had also visited the patient at their home for a pre-assessment check. The conversations about the research being conducted were also facilitated by the

family caregivers – at home and in the clinic. Carers were involved in the assessment of mental capacity for potential participants and often played a facilitative role in the consent process, completing the baseline questionnaire and in the qualitative interviews. The facilitative role that caregivers played in the research process mirrors the "Family caregivers as witnesses and advocates" theme in the qualitative findings.

During the research process, the clinical staff and carers were 'gatekeepers' in accessing potential participants which is appropriate when recruiting from a vulnerable patient population (395). The interest in and acceptance of the research by the caregiver often benefits the researcher as they add credibility to the research – in this case the PACE study and my PhD specifically. Gatekeepers' coperation with the research is often influenced by what they perceive as a benefit or a threat to participation (396). Only in a few cases did I witness an obstructive gatekeeper and this occurred when a carer did not want to share personal or sensitive information or when they perceived that their involvement would add a burden to their work load or carer responsibilities (395).

The family caregivers' contributions during the qualitative interviews were valuable in the practical aspects of setting up interviews and in building rapport at the start of the interview process. Their input was important, especially where the patient was forgetful or confused about timescales and onset of symptoms. Family caregivers also provided important context in terms of family dynamics, dietary habits and practices as well as interactions with healthcare professionals and services. Whilst, this was valuable to me as the researcher it was clear that for some family caregivers, taking part in the research process was empowering and gave them an opportunity to share their experiences and insights, and this is reflected in the literature where carer involvement has been expressed as being "therapeutic" (397).

Finally, when designing the qualitative research component of this mixed methods project, I chose to use thematic analysis. The reflexive thematic analysis used an

inductive approach where theme development came from the data. Coding was at a more *semantic* level where the analysis explored meaning at the more explicit or surface level which is ideal for a descriptive study. The systematic review identified no cachexia studies in primary care settings. So, when the study changed focus to UWL related to cachexia, I kept the coding and analysis at the descriptive level due to the scarcity of qualitative studies in this clinical setting and in this patient population. The qualitative framework for this study, as described by Braun and Clarke, was *experiential* where the analysis aimed to capture and explore participants' experiences, perspectives and sense-making and the theoretical framework leaned towards *critical realism* – where analysis aimed to capture the reality of truth as expressed in the data through the participants' experiences (201). Therefore, from a critical realist standpoint, truth and reality is shaped by language and culture and the lived experience. Thus, this inductive, semantic, experiential and critical realist approach was appropriate for a more descriptive analysis of qualitative data which reflected the experience of a phenomenon – unintentional weight loss – from the perspective of participants and their caregivers.

From the beginning of my applied health researcher career, I considered myself a realist and have been trained to use positivist methods. Mid-way through my research career I started to use post-positivist methods, with an evidence-based approach of data gathering and triangulation, accompanied by focus groups and semi-structured interviews. My experience as a mixed methods researcher, therefore, has mainly been reflected in quantitative studies with qualitative elements to corroborate and provide insight to quantitative findings. This study was similar but with a dominant qualitative study which allowed me to adopt a pragmatic paradigm and to use a critical realist approach.

6.11 Summary

This chapter described the results from the patient and caregiver interviews and described their experiences of unintentional weight loss. The themes derived from the thematic analysis indicate the importance of loss of appetite, perception about

the nature of the weight loss and its association with chronic conditions, also the influence of family and caregivers on seeking healthcare.

There were five themes developed from the thematic analysis of the interview data:

(1) Experiences and perceptions of appetite loss

Appetite loss was often rationalised (due to physical inactivity, associations with ageing) and normalised if longstanding. The loss of appetite often led to changes in dietary intake, habits and food preparation.

(2) Knowledge, belief and concerns about UWL

This theme and sub-themes describe the influential factors that contribute to participants' perceptions as to the causes of UWL. Participants are in a patient cohort who often have complex medical histories and it can be unclear why they are losing weight. Loss of memory can affect participants' recollection of timescales with respect to weight loss and onset of symptoms. Additionally, health literacy and previous experiences can influence participants' awareness of the significance of UWL.

(3) Experiences and perceptions of UWL

There was a mirroring of the rationalisation and normalisation that was seen with appetite loss. Weight loss was often perceived as being a positive thing especially in those who were currently overweight or who had been overweight. This led to the development of a sub-theme exploring the experience of UWL in those who are overweight or obese where the signs of UWL can be hidden and confused with periods of intentional weight loss. Whilst weight loss was perceived as positive – the resultant loss of strength and function associated with losing muscle mass (and with getting older) was a concern that was mentioned by a number of participants.

(4) Family caregivers as witnesses and advocates

Family caregivers played an important role in the practicalities of meal preparation and encouraging participants to maintain eating habits. This was especially important when participants minimized their weight loss and did not mention it to healthcare professionals. Family caregivers seemed more concerned than participants possibly due to being witnesses to the onset and impact of changes.

They were instrumental in pushing for UWL being addressed in healthcare consultations,

(5) Help seeking for UWL responses from health care professionals.

Minimisation of UWL and loss of appetite can lead to a lack of concern about UWL. There was concern if the UWL was sudden, without explanation and if severe enough to change one's appearance to a significant extent. There were expectations that once participants sought healthcare input that there would be further investigations and referrals. However, participants and caregivers also described barriers to seeking help – such as lack of access to appointments and difficulties encountered in communicating concerns. Finally, the response of healthcare professionals to weight loss was generally positive, irrespective of the unintentional nature of the loss. This positive reinforcement and apparent lack of concern reinforces the positive benefits of weight loss to participants.

The next chapter (Chapter 7) will discuss the integrated findings from the systematic review, quantitative and qualitative phases of this PhD project.

7 Mixed methods results

7.1 Introduction

This chapter describes the findings of the data integration, which was conducted on three levels: (1) cross-referencing of some of the quantitative findings with the qualitative interview data; (2) mapping the key qualitative and quantitative findings to visualise an adapted patient delay pathway; and (3) integration of findings from the quantitative and qualitative phases to assess how well the qualitative data explained the quantitative findings and for any agreement of the findings. These data integration approaches were used to answer RQ 16: How is UWL assessed and managed in primary care and experienced by older patients who might be at risk of developing cachexia?

7.2 Findings from the mixed methods phase

7.2.1 Summary of quantitative and qualitative findings

There were 15 qualitative interviews were conducted with 14 patient participants and seven caregivers. A summary of their key quantitative and qualitative findings is reported in Table 27. The average age of the interview participants was 77.4 years old, and their mean weight and BMI were 67.78 kg and 25.81 kg/m^2. The percentage of weight loss in the previous year varied from 0 to 23.16%. As classified by the ACE-27 classification, the number of comorbidities ranged from two to nine conditions. Two participants had cancer (current cancer or previous history of cancer) included in their ACE-27 list of comorbidities.

The median Rockwood Clinical Frailty Scale score was 6 (Moderately frail: People need help with all outside activities and keeping house), and the median AKPS functional status score was 65. A patient with an AKPS of 60 is assessed as being able to care for most needs but would require occasional assistance, while a patient with an AKPS of 70 is assessed as able to care for themselves but unable to continue normal activity or to do active work.

The interview participants were younger than those in the PACE study (mean age 77.4 years vs 81.6 years). They weighed less than the PACE study participants (67.78 kg vs 76.49 kg). They were similar to the 24% of participants who reported UWL in that they were frailer than PACE study participants who had not experienced UWL (mean Rockwood CFS of 5 vs 6). The interview participants had a higher mean number of comorbidities using the ACE-27 classification compared to the whole PACE study cohort (4.93 vs 4.34).

In the qualitative interviews, most participants reported a change in appetite loss, which broadly corresponded with their responses at the ICC when recruited. Only one participant reported no loss of appetite in the previous week (IPOS appetite score 'Not at all'), which was explained in the interview as temporary loss of appetite and weight loss caused by colorectal cancer that was detected and treated relatively quickly. At the point of the interview, this participant started to regain weight, and his appetite returned to normal.

As reported in the interviews, the health and functional status of the interview participants showed that participants had a number of comorbidities, which generally correlated well with the number of comorbidities (as listed in the ACE-27 classification of conditions). There was one outlier - a participant with nine conditions who only mentioned a few of them during the interview and did not mention a history of cancer, as recorded in the notes. In terms of functional status, most of the participants had some form of mobility issue, which was either explicitly mentioned by the participants or linked to a chronic condition that they disclosed.

The experience of unintentional weight loss varied among the interviewees. Nearly half of the participants (n = 6/14) linked their weight loss to prolonged hospitalisation or multiple hospital stays. Others reported that the loss of weight originated with a bereavement (n = 2/14), suspected or confirmed cancer (n = 3/14) and no clear trigger (n = 3/14). The family was concerned about the speed and

severity of the weight loss, while the patient was concerned mainly about a changed appearance (perceived older-appearing face) and/or muscle weakness.

Most participants received assistance with grocery shopping, meal preparation and help with other daily living activities. Several arrangements were reported for meals, such as meal delivery, and participants reported a loss of enjoyment with food preparation and eating. Some participants' eating habits were altered due to a loss of appetite (smaller portions, missing out on a meal).

In this patient cohort, interactions with healthcare professionals regarding the participants' weight loss also varied. A number of participants had reported their UWL, while others had not due to a lack of concern about weight loss. Participants downplayed the role of dietary supplementation, prescribed or recommended by their GP, and whether or not they had been referred to another service for treatment (e.g. dietetic service) or further investigation.

Table 27: Summary of quantitative and qualitative findings for the interview participants

	Quantitative data							**Qualitative themes**				
ID	***Age/sex***	***Rockwood CFS***	***Lives with***	***BMI***	***Weight loss %***	***Weight measurements***	***ACE 27 – number of comorbidities***	***Loss of appetite***	***Health and functional status***	**UWL experience**	**Dietary habits**	**Healthcare interactions**
36	80 F	5	S/P	20.38	20.73	6	5	No loss of appetite reported ***IPOS*** *Not at all*	Physical mobility issues and OT input. COPD, arthritis, CKD, gastric ulcer, AF, AI skin disease. Polypharmacy	Post-hospitalisation and continued WL >20 kg, concerned about the loss of strength, some weight gain since	Private meal preparation arrangement, partner and family support for some ADL	Telehealth service protein drinks prescribed for weight loss.
46	83 F	6	S/P	25.79	5.14	3	4	Loss of appetite reported – mainly from partner ***IPOS*** *Severely*	Polypharmacy – blames medication for some loss of appetite, issues with memory	Unreliable witness of weight loss history, partner concerned about the speed of weight loss	Partner shares household chores and cooking, eats high-fat meals and dairy	Help-seeking-for weight loss coincided with ICC referral, has had dietary supplementation prescribed.
47	87 F	5	Alone	18.55	5.94	1	3	Acceptance of age-related loss of appetite. ***IPOS*** *Slightly*	HF and Type 2 Diabetes that improved with weight loss	Lost weight after their spouse died six years ago but seems to be still losing some weight in the previous year.	Fiercely independent, shops and cooks own meals. Reduced dietary intake	Positive reassurance from GP and practice nurse about WL, no weight gain advice given.

	Quantitative data							Qualitative themes				
ID	*Age/sex*	*Rockwood CFS*	*Lives with*	*BMI*	*Weight loss %*	*Weight measurements*	*ACE 27 – number of comorbidities*	*Loss of appetite*	*Health and functional status*	UWL experience	Dietary habits	Healthcare interactions
										Concerned about WL changing appearance and ageing her		
61	73 F	4	S/P	31.90	0.23	1	5	Reported that she had regained her appetite ***IPOS*** *Moderately*	Type 1 Diabetes, – amputee, pancreatitis, hepatitis, renal failure, appendicitis, Alzheimer's dementia	Periods of dieting but UWL due to a series of GI illnesses and hospitalisation, concerned more about the loss of strength	Dieting on and off for many years; partner does some of the cooking	Advised to lose weight so is not concerned about the UWL.
65	71 F	3	S/P	23.61	*Blank*	*Blank*	2	Reported some loss of appetite ***IPOS*** *Moderately*	Gastric ulcer, IBS	UWL dramatic and noticeable; no clear trigger, concerned as to cause—possibly cancer, also felt that WL had aged her	Pleased not to have to cook for the family anymore, does not eat with enjoyment	Colleagues encouraged her to seek help, GP was shocked at the appearance and run several tests.
68	80 M	5	Alone	24.16	13.18	8	5 (cancer)	Regained some weight and appetite ***IPOS*** *Not at all*	Previous cancers, current prostate cancer, COPD and memory loss	Dramatic weight loss and loss of appetite, marked change in appearance and was very obvious	Generally, a good appetite; cooks for himself	Difficult to get a GP response to weight loss, carer advocated for the patient. Discussed WL

	Quantitative data							Qualitative themes				
ID	*Age/sex*	*Rockwood CFS*	*Lives with*	*BMI*	*Weight loss %*	*Weight measurements*	*ACE 27 – number of comorbidities*	*Loss of appetite*	*Health and functional status*	UWL experience	Dietary habits	Healthcare interactions
										to friends and family		with pharmacist who referred him to the ICC.
131	87 F	7	Family	16.21	17.65	5	7	Reported loss of appetite in interview. Not regained since hospitalisation. ***IPOS*** *Moderately*	Chronic heart failure, poor mobility	Post hospitalisation weight loss	No energy to cook and family nearby to support with ADL	Dietitian, protein drinks. Family concerns about physical deterioration and have followed up with GP.
132	65 F	6	Alone	39.12	0.00	3	4	Reported some loss of appetite. ***IPOS*** *Overwhelmingly*	Hip joint issues, arthritis, spinal issues, chronic pain, previous breast cancer, mental health issues	History of dieting. Reported UWL, but no documented WL in case notes in the past year, possible weight fluctuation	Lost enjoyment of food; sometimes feels sick when she eats	Needs to lose weight for referral for second hip surgery and possible bariatric surgery.
178	66 M	6	Alone	22.05	9.59	7	6	Regained appetite and started to regain weight	Colorectal cancer, Type 2 Diabetes, poor mobility,	Rapid UWL and loss of appetite, treated quickly for colorectal cancer	Meal on wheels and family support, microwaves	Investigated quickly for UWL, family concerns about

	Quantitative data							Qualitative themes				
ID	*Age/sex*	*Rockwood CFS*	*Lives with*	*BMI*	*Weight loss %*	*Weight measurements*	*ACE 27 – number of comorbidities*	*Loss of appetite*	*Health and functional status*	UWL experience	Dietary habits	Healthcare interactions
								IPOS *Not at all*	chronic venous ulceration		quick meals and eat sandwiches	appearance and loss of appetite so pushed for tests and treatment.
190	85 F	6	Alone	15.57	5.66	8	4	***IPOS*** *-Severely*	Chronic HF. Mobility issues	Post hospitalisation weight loss	Has regained some weight and some appetite; now eats snacks as well as meals	Dietitian input and protein milks; regularly weighed by carers and HF nurses
195	77 F	6	S/P	31.35	1.52	3	9 (cancer)	***IPOS*** *Slightly*	Diabetes, CVS issues, osteoporosis, chronic immobility	UWL - lost relatively quickly, due to hospitalisations, gall bladder and GI issues and some disordered eating habits, loss of muscle strength	Eating disorder in the past, limited range of vegetarian food eaten; does not like to eat three meals	Seeking dietitian input but conflicted as to what she thinks they can do for her; not keen to eat three meals a day or gain weight
237	69 F	-	S/P	42.16	1.19	1	6	Some loss of appetite	Arthritis, hallucinations, chronic pain, CVS issues,	WL could be due to weight fluctuations.	Eating less at mealtimes – e.g. sandwiches	Not concerned about WL and not sought help for it; has

	Quantitative data							Qualitative themes				
ID	*Age/sex*	*Rockwood CFS*	*Lives with*	*BMI*	*Weight loss %*	*Weight measurements*	*ACE 27 – number of comorbidities*	*Loss of appetite*	*Health and functional status*	UWL experience	Dietary habits	Healthcare interactions
								IPOS *Moderately*	diabetes, kidney disease			been encouraged to lose weight in the past
238	77 F	5	S/P	19.07	5.05	1	5	Has slowly regained some appetite ***IPOS*** *Slightly*	Rheumatoid arthritis, breathlessness, investigated for COPD	Loss of appetite and weight loss after husband died four years ago; has always been slim	Missing evening meals, bought herself some protein drinks	Not concerned about WL enough to seek medical advice, had investigations for COPD and lung cancer due to breathlessness and was a smoker
252	79 F	7	Other	31.39	23.16	4	4	Severe loss of appetite and loss of enjoyment of eating ***IPOS*** *Severely*	Long term mental health issues, diabetes, severe mobility issues	UWL due to long hospitalisation for pneumonia. Severe muscle weakness: finds it difficult to get out of bed and to sit upright	Care home resident, has to be coaxed to eat	Not sure who her GP is now that she is in a care home; more concerned about muscle weakness than WL

** ACE-27: Adult Comorbidity Evaluation; AF: atrial fibrillation; AI: Autoimmune; CFS: Clinical Frailty Scale; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CVS: cardiovascular system; GI: Gastrointestinal; HF: heart failure; IBS: Irritable bowel syndrome; ICC: Integrated Care Clinic; IPOS: Integrated Palliative Care Outcome Scale (Appetite score); OT: occupational therapist; S/P: Spouse or partner; UWL: unintentional weight loss; WL: weight loss*

7.2.2 Integrated results – mapping patient and treatment delays

7.2.2.1 Adapted Andersen model of total patient delay

The Andersen's model of total patient delay was adapted and used as an additional integration method to bring together the qualitative themes and quantitative findings. This framework was used more as a mapping tool to visualise the patient journey from the onset of UWL, as described in the data (Figure 7). Andersen's model of total patient delay was adapted to reflect the journey in primary care only, and the referral and diagnostic stages were not seen in the original model. Normally, the diagnostic phase is dependent on the patient's journey through the healthcare system, but in this adapted version of the model, the diagnostic phase is classified as the 'primary care response'.

The patient journey was described mainly from the family and caregiver perspectives through the qualitative interviews. By contrast, the data from the case note review were used to describe the extent of weight measurements in routine primary care consultations and the clinical response to documented weight loss. The patient journey from the healthcare professional perspective is missing. However, the healthcare system and healthcare professional actions were mapped where the qualitative data cross-referenced or where relevant information was available from the quantitative case note review.

With respect to the case note review data, this patient cohort was weighed regularly; however, this routine weight monitoring was not necessarily linked to weight loss. Most participants had six-month or annual reviews for their chronic conditions and would be weighed in those consultations. Some participants reported that they were weighed in response to weight loss; however, on one occasion, a participant reported their GP's reaction to their appearance as the UWL was obvious. Conducting blood tests seemed to be a common response to investigating weight loss and this was also correlated in patient interviews.

Data from the literature could have been used to map the healthcare professional perspectives. This would have involved the review of the qualitative literature

which captured perspectives of primary care health professionals managing malnutrition or muscle wasting in this patient population.

7.2.2.2 Appraisal delay

The patient and caregiver perspectives, as described in Chapter 6, show that participants and their caregivers had processed their UWL and assigned possible causes (Figure 7). The potential causes of UWL could be obvious (e.g. due to hospitalisation) or more difficult to identify. The participants' views on why they were losing weight led to their perceptions of the benefits of weight loss and any positive feedback that they had received from others, such as healthcare professionals. Participants related their thoughts of underlying causes when they received cues from the healthcare professionals that they mentioned. For instance, participants sometimes linked weight loss to polypharmacy if their GP looked at and reviewed their medication. The medical review was sometimes perceived as a response if there were issues with polypharmacy, and even if the review was routinely conducted – for instance on an annual basis or when it was conducted for all patients as part of the ICC assessment.

The appraisal of UWL as a symptom of concern is a complex process, as can be seen from the number of help-seeking barriers and facilitators included in Figure 7. There was a great deal of overlap in these factors and combined with the lack of concern and rationalisation of symptoms means that help-seeking behaviour is often delayed.

7.2.2.3 Illness, behavioural and scheduling delays – identification of a problem and reporting a problem

The next three delay stages (illness, behaviour and scheduling) in the original Andersen model corresponded with the interview participants identifying that their UWL was a problem and that it might need to be reported to a healthcare professional. There is some overlap in processing the possible causes of and identifying UWL as a problem. Participants' rationalisations of the possible causes

of UWL and their perceptions of the possible benefits alongside their previous experiences of UWL in themselves and family members were all factors that contributed to help-seeking behaviour. Additionally, the markers of weight loss that needed medical attention were generally well known in this cohort of interview participants. Unintentional weight loss that occurred suddenly, '*out of nowhere'*, without a clear cause '*for no reason'* and that became dramatically evident '*clothes were hanging off her'* would be something that they would need to seek medical intervention. This was especially true if they or their loved ones thought that the weight loss was due to a suspected cancer. Sustained or gradual weight loss was something participants normalised but also reported that if they could not regain weight, they would be concerned. This concern, however, did not always lead to help-seeking, but if relatives or caregivers were worried, this would sometimes be escalated.

7.2.2.4 Scheduling delay – reporting a problem

This delay stage in the original model describes the time taken to act on the decision to seek help and actually attend an appointment. What became clear in the interview data was that participants and caregivers felt that external or healthcare-related factors were often responsible for the delay encountered when trying to seek help. Some participants reported difficulties accessing primary care appointments due to busy GP practices. Also, the challenges in keeping the UWL a prioritised issue were mentioned. This was especially the case if the participants felt that they had a number of symptoms or issues to be communicated or attended to. One participant was told by their GP that they had to investigate or attend to other issues before addressing the reported weight loss.

7.2.2.5 Treatment delay – response to the UWL, diagnosis of the underlying cause and management of the UWL or underlying cause

When participants and caregivers discussed the healthcare response to UWL, it started with an expectation of action from their primary care providers if weight loss was something to be concerned about. They expected further investigations

and possibly a referral to secondary care to either identify or treat the underlying cause. In a number of ways, the participants reported that the healthcare professionals responded to their weight loss. They would either start identifying the weight loss as a problem through investigations (see appraisal delay above), reassure patients, affirm the positive benefits of losing weight or provide guidance as to the benefits of weight loss to their underlying condition. The case note review data showed that once the primary care healthcare professional (most likely the GP) identified that UWL was a problem, they could start investigations for the underlying cause or refer the patient for further investigations or treatment. This correlated with the patient interviews regarding what they would expect their GP to do once a problem was detected. What GPs would commonly do, however, was prescribe or recommend dietary supplementation to participants. They would also commonly refer participants to the dietetic service. This was not often reported in participant interviews – participants would mention protein drinks, but they would need to be followed up to recall whether this had been prescribed (or recommended) by their GP or by a dietitian.

The next section reports the integration of the findings from the quantitative and qualitative phases.

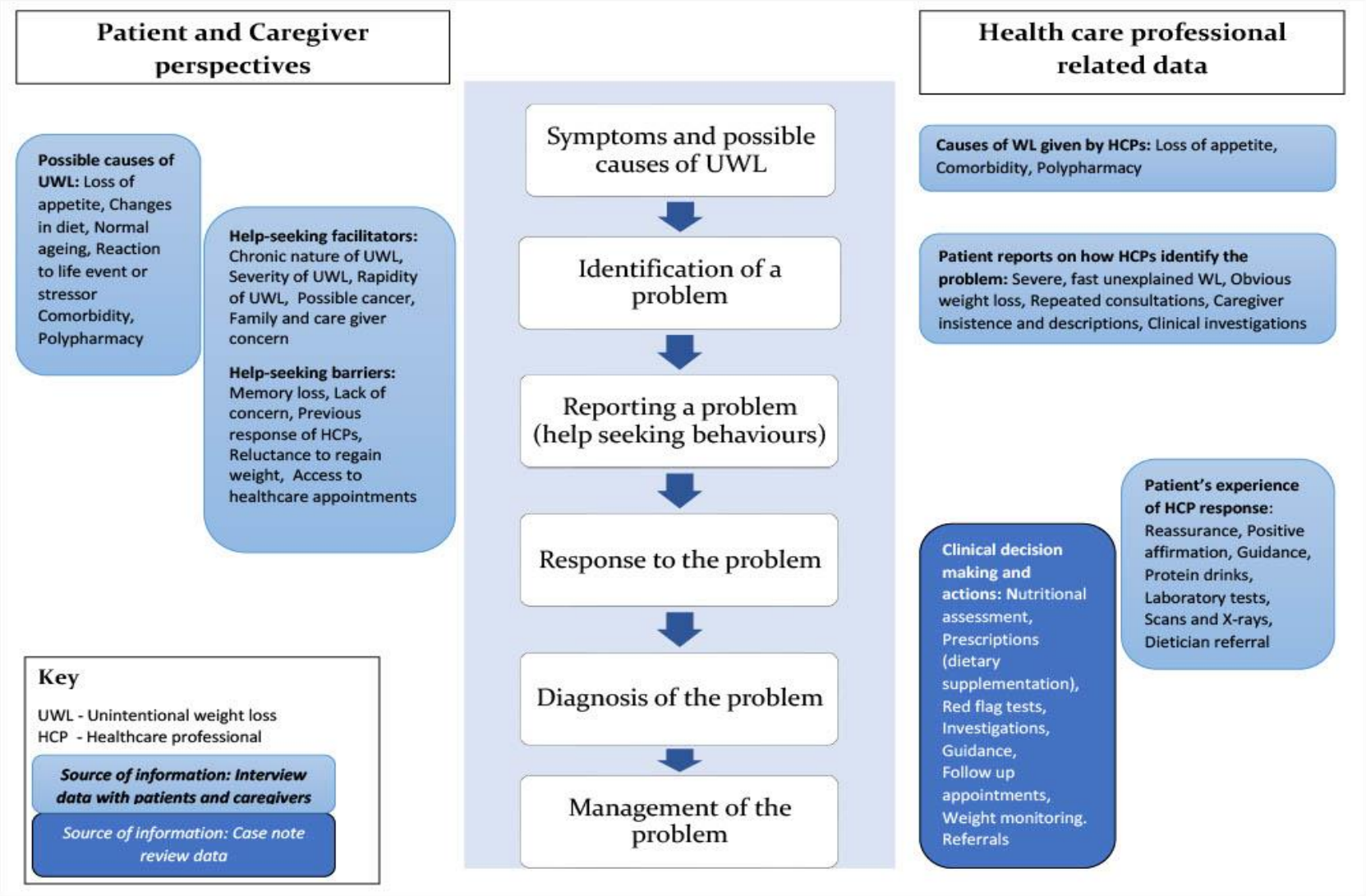


Figure 7: Factors associated with initial presentation and management of UWL in primary care –adaptation of Andersen's model of total patient delay

7.2.3 Integrated quantitative and qualitative themes

7.2.3.1 Integrated findings presented in the convergence coding matrix

A convergence coding matrix, as described by Farmer et al. (202), was used to integrate the findings of this PhD study. The findings of the systematic review, the quantitative themes, and the qualitative themes and sub-themes were compared and cross-referenced. The data integration and triangulation contributed to the development of five meta-themes that are reported in Table 28: (1) loss of appetite as an ambiguous indicator in primary care settings; (2) perceived benefits of UWL and prioritisation of concerns; (3) lack of concern about UWL and help-seeking; (4) role of family caregivers in reporting UWL and seeking healthcare intervention for UWL; and (5) healthcare professionals' role and clinical response when UWL is a concern.

For each theme, there was an assessment of where, across the findings from each study phase, there was 'agreement', 'partial agreement', 'dissonance', (disagreement) or 'silence'. Silence occurs when findings for a topic area or theme exist in one set of data but are absent in another.

7.2.3.2 Loss of appetite as an ambiguous indicator in primary care settings

There was silence across the findings for the three study phases when they were integrated. There was partial agreement across the datasets for all four quantitative themes with the qualitative theme 'Experiences and perceptions of appetite loss associated with UWL'. Around 50% of baseline survey participants who reported UWL had 'poor' or 'very poor' appetite, and there was a significant difference in appetite in the past week reported by those who reported UWL than participants without UWL. The loss of appetite was associated with a self-report of UWL, and the loss of appetite to a severe or overwhelming extent in the previous week was associated with a management action in the previous 12 months to address UWL. The assessment of appetite was a common management action plan documented in clinical appointment notes, and this was routinely assessed by healthcare professionals. In comparison, while the majority of interview participants had

noticed appetite loss (sometimes quite severe loss), there was also an acceptance and normalisation of the appetite loss described in the interviews.

7.2.3.3 Perceived benefits of UWL and prioritisation of concerns

There was silence across the findings for the three study phases when they were integrated. There was partial agreement across the datasets for the quantitative theme 'The nature of self-reported UWL' and the qualitative theme 'Experiences and perceptions of UWL'.

In the case note review, participants with self-reported UWL weighed less and were more likely to be underweight or normal weight than participants who had not reported UWL. These participants were mostly (64.3%) not worried about their weight loss. What was illustrated in the qualitative dataset was how some participants perceived losing weight to be a positive thing, especially if they had been trying to lose weight since early adulthood. There seemed generally more accepting of a lower weight status – 'normal weight' or 'underweight'. Participants also reported some perceived benefits of weight loss, which was often justified by describing how healthcare professionals responded positively and encouragingly to their weight loss. Furthermore, some participants, while acknowledging that they had lost a significant amount of weight, were more concerned about changes in appearance and loss of strength and function rather than about the weight loss itself.

7.2.3.4 Lack of concern about UWL and its impact on help-seeking

There was silence across the findings for the three study phases when they were integrated. There was agreement across the datasets for the quantitative theme 'Self-reported UWL and associations with documented UWL' and the qualitative theme 'Help-seeking for UWL – barriers, enablers and responses from healthcare professionals'.

Participants who had reported UWL in the past year were mostly (64.3%) not worried about their weight loss. The proportion of participants correctly reporting UWL decreased when they had significant documented weight loss (over 5%) in

the past year compared with those who had any documented weight loss. This correlates with interview data, where help-seeking and reporting UWL was minimised if UWL was sustained. There was acceptance of the change in body weight status over time, and these participants were probably less likely to report UWL in the previous 12 months. Participants who were classified as obese (using BMI ranges) were also less likely to report UWL in the previous 12 months.

Participants were most likely to seek medical intervention for UWL if it was severe and rapid in nature, with no clear triggers. This was reported as suspicious, and it was felt that this type of UWL would need an investigation or referral to ascertain the underlying cause of the weight loss. If weight loss was perceived as temporary or a response to an acute life event, then participants reported it in routine appointments, such as disease reviews. That is, they were less likely to book an appointment with their GP to discuss it. The interview data suggests, however, that if the weight loss was sustained (i.e. if their appetite or weight loss was not regained), then there was an acceptance of this new normal and adaptations were made to diets and meal preparations to reflect this change. The qualitative data also suggested that help-seeking behaviour was encouraged or undertaken by concerned family caregivers. This is reflected in the meta-theme 'Role of family caregivers in reporting UWL and seeking healthcare intervention.'

7.2.3.5 Role of family caregivers in reporting UWL and seeking healthcare intervention

There was silence across the findings for the three study phases when they were integrated. There was agreement across the datasets for three quantitative themes: 'The nature of documented UWL', 'Self-reported UWL and associations with documented UWL', Weight loss measurements and management of UWL as recorded in the primary care records in a 12-month period' and the qualitative theme 'Witness and advocacy roles of family caregivers'.

The value of living with a spouse/partner or family caregiver was reported in both datasets. When participants mentioned their weight loss to at least one other person, they mainly mentioned it to their spouse, family member or friend.

Participants who lived with a spouse or partner were less likely to have significant documented weight loss. Living situation was a variable possibly associated with a self-report of UWL. Those who lived alone and had documented weight loss were less likely to have a management action plan in their notes than those who lived with others. All of this was echoed strongly in the qualitative dataset where the participants' and caregivers' interviews demonstrated the level of input caregivers (and sometimes non-resident family members) had in ensuring that weight loss and loss of appetite was reported. Family caregivers reported the need to be persistent in pushing for intervention if they were concerned. They also mentioned the need for their advocacy, especially for participants who had memory issues or who were not as concerned about weight loss.

7.2.3.6 Healthcare professional role and clinical response when UWL is a concern

There was silence across the findings for the three study phases when they were integrated. There was partial agreement across the datasets for the quantitative theme 'Weight loss measurements and management of UWL as recorded in the primary care records in the previous 12 months' and the qualitative theme 'Help-seeking for UWL – barriers, enablers and responses from healthcare professionals'. The data integration of the datasets showed agreement at one level and partial agreement at two levels.

Normal weight measurements: There was full agreement at this level across the quantitative and qualitative datasets. Most participants had at least one weight measurement recorded in their case notes in the previous 12 months. Qualitative interview data showed that participants were routinely weighed for disease and medication reviews in primary care consultations. The majority of documented weight measurements were in consultations with nursing staff, which was also echoed in the qualitative dataset.

Healthcare professional roles and responses to UWL: There was partial agreement at this level across the quantitative and qualitative datasets, as this was explored in the qualitative interviews but was described differently in the quantitative

findings. There was an expectation that healthcare professionals would escalate a response to UWL that was of concern. There was evidence in the qualitative dataset that there was sometimes a feedback loop with respect to the participants' concerns about their UWL. Their concerns could be diminished or justified depending on the healthcare professional's response. This then impacted their help-seeking behaviours. Some participants mentioned receiving a positive response to their weight loss. The healthcare professional's role in these situations was to provide reassurance, but some responses tipped over into encouragement of continued weight loss, especially if it was perceived to be of benefit to a chronic condition (e.g. type 2 diabetes), and if the participant was overweight or obese before losing weight.

The quantitative findings, in contrast, identified the ways in which healthcare professionals responded to documented weight loss. The number of weight measurements documented in the notes almost doubled if there was significant documented weight loss in the notes that indicated that healthcare professionals recognised and monitored significant weight loss (≥5%). Factors associated with a management action in the case notes were the participants' characteristics that represented poor physical and functional statuses and outcomes. Participants who reported severe loss of appetite and were underweight or had a normal weight status using BMI ranges were also more likely to have a management action documented in their notes to address their UWL. They were less likely to have management action in their notes if they were overweight, obese and severely obese. The findings across the qualitative and quantitative datasets indicated that a lack of concern from both patient and healthcare professional perspectives impacted help-seeking behaviour, and the clinical responses to UWL, especially when the weight loss was not highly evident, was deemed to be temporary or was perceived to be beneficial.

Table 28: Agreement between quantitative and qualitative themes and development of mixed methods inferences

META-THEME: Loss of appetite as an ambiguous indicator in primary care settings			
Systematic review	**Quantitative results**	**Qualitative findings**	**Agreement or dissonance?**
The patient population in the narrative synthesis and from the PACE study were different. Additionally, no studies were reported as being conducted in primary care settings. However, several studies assessed pre-cachexia on admission or referral to secondary or tertiary care assessed for anorexia - 8 / 18 pre-cachexia studies. The cachexia definitions that included anorexia in pre-cachexia assessments were Muscaritoli 2010 (10)and Fearon 2011 (9), One of the included studies (354) conducted in a hospital setting,	**Theme 1: The nature of self-reported UWL** Baseline survey: 49.3% of participants who reported UWL had 'poor' or 'very poor' appetite. IPOS appetite scores: significant differences in appetite in past week reported by those who reported UWL – to a moderate (p = 0.027), severe and overwhelming extent (p<0.001) than participants without UWL. **Theme 2: The nature of documented UWL** Characteristics of participants with significant documented weight loss in the past 12 months Loss of appetite to a severe or overwhelming extent in the previous week	**Theme: Experiences and perceptions of appetite loss associated with UWL** Normalisation and rationalisation of reported appetite loss *Appetite loss associated with ageing and changes in lifestyle (post retirement and changes in family dietary routines)* *Acceptance of fluctuations in appetite due to life stressors, acute events and temporary circumstances (e.g. hospitalisations)*	Silence across the three study stages Partial agreement across the quantitative and qualitative themes.

assessed geriatric inpatients for cachexia, frailty, malnutrition and sarcopenia. Anorexia was assessed by the Evans' diagnostic criteria used to identify cachexia (8).	**Theme 3: Self-reported UWL and associations with documented UWL** Loss of appetite in the previous week was possibly associated with a self-report of UWL **Theme 4: Weight loss measurements and management of UWL, as recorded in the primary care records in a 12-month period** Factors associated with a management action in the case notes in the past 12 months: - Loss of appetite to a severe or overwhelming extent in the previous week		
META-THEME: Perceived benefits of UWL and prioritisation of concerns			
Systematic review	**Quantitative results**	**Qualitative findings**	**Agreement or dissonance?**
Studies included in the narrative review were not assessed on the perceived benefits of UWL. Most patients in these studies were undergoing treatment for cancer.	**Theme 1: The nature of self-reported UWL** Comparison of participants with and without self-reported UWL – those with UWL had a mean weight of 65.5 kg vs 80.1 kg (p<0.001) and were more likely to	**Theme: Experiences and perceptions of UWL** *Periods of UWL linked to triggers – bereavement and prolonged hospitalisation, where weight loss was sustained, there was acceptance of new weight status*	Silence across the three study stages Partial agreement across the quantitative and qualitative themes.

When patients were being assessed for cachexia in secondary or tertiary care settings, UWL was perceived as being deleterious to the patient and their outcomes when receiving treatment.	be underweight (BM<20 kg/m²) or normal weight (BMI 20–20.49 kg/m²) Of the participants who had not reported UWL, more were obese compared with those who reported UWL (39.3% vs 16.7%, (p = 0.001) Baseline survey: 31.4% of participants who reported UWL were concerned about their weight loss Baseline survey: 44.4% who reported UWL thought that they had lost over a stone (>6.35 kg) in the past 12 months.	*A weight status of 'underweight' or 'normal weight' was better than being 'overweight' or 'obese', and concerns were mainly raised with change in appearance and loss of strength and function rather than with weight loss.* *Participants who were overweight or obese had lost weight unintentionally, but some participants perceived it as being due to a temporary cause.*	
META-THEME: Lack of concern about UWL and impact on help-seeking			
Systematic review	**Quantitative results**	**Qualitative findings**	**Agreement or dissonance?**
UWL related to cachexia is very concerning to patients and clinician. More oncology centres are instituting cachexia and nutrition protocols as part of cancer care. However, no qualitative interviews on help-	**Theme 1: The nature of self-reported UWL** Baseline survey: 31.4% of participants who reported UWL were concerned about their weight loss. Of the participants who had not reported UWL, more were obese	**Theme: Help-seeking for UWL – barriers, enablers and responses from healthcare professionals** *Help-seeking and reporting of UWL was perceived as important when weight loss was sudden and severe without a trigger or perceived cause. Otherwise, sustained weight loss and a change in body weight status were sometimes accepted if dietary*	Silence across the three study stages Partial agreement across the quantitative and qualitative themes.

seeking behaviour for cachexia-related UWL were included in the narrative review.	compared with those who reported UWL (39.3% vs 16.7%, (p = 0.001). **Theme 3: Self-reported UWL and associations with documented UWL** The proportion of those who did not report UWL but did have documented weight loss was 55.6% (100/180 participants). 44.8% (26/58 participants) of the participants who did not report UWL but had documented weight loss (≥5%).	*changes and supplementation did not reverse the loss.* *Help-seeking for UWL* - *Suspected cancer* - *Reaction or concern from other people* - *Temporary weight loss* - *Lack of concern*	
META-THEME: Role of family caregivers in reporting UWL and seeking healthcare intervention			
Systematic review	**Quantitative results**	**Qualitative findings**	**Agreement or dissonance?**
No studies included in the narrative synthesis had detailed data on carers or on their caregiver roles. There are a number of qualitative studies examining the impact of cachexia on family caregivers and their experiences.	**Theme 2: The nature of documented UWL** Participants who lived with a spouse or partner were less likely to have significant documented weight loss than those who had other living situations (30.5% vs 45.2%, p=0.046%).	**Theme: Witness and advocacy roles of family caregivers** *Living situation: Those with family caregivers witnessing appetite loss and weight loss advocated for medical intervention and were persistent in mentioning symptoms in healthcare interactions. They also advocated for medical intervention such as investigations, referrals and treatment.*	Silence across the three study stages Partial agreement across the quantitative and qualitative themes.

However, no qualitative studies were identified for inclusion in the narrative synthesis as they did not report an assessment for cachexia. Patients and caregivers were often approached to participate in these studies when cachexia was evident.	**Theme 3: Self-reported UWL and associations with documented UWL** The variables possibly associated with a self-report of UWL were living situation, documented weight loss, significant documented weight loss (≥5%) and loss of appetite in the previous week. **Theme 4: Weight loss measurements and management of UWL as recorded in the primary care records in a 12-month period** Participants who lived alone were less likely to have a management action than those who lived with others (27.9% vs 44.33%, p<0.004). Baseline survey: When participants mentioned their weight loss to at least one other person – 32.3% mentioned it to their spouse, family member or friend. Baseline survey: Over half (63.2%, n = 43/68) had been weighed by a healthcare professional, spouse,	*Caregivers reported helping to schedule appointments; they helped participants with the practical aspects of attending consultations, were persistent in mentioning symptoms (see above meta-theme) and pushed for referrals and investigations. This was especially true if the participants had memory issues.* *There was also an expectation expressed by some participants and caregivers that they would expect investigations and referrals to secondary care if UWL had a suspected serious underlying cause.*	

	family member or friend in the past year.		
META-THEME: Healthcare professional role and clinical response when UWL is a concern			
Systematic review	**Quantitative results**	**Qualitative findings**	**Agreement or dissonance?**
No studies included in the narrative synthesis were conducted in primary care settings. However, more recently published cancer studies reported the implementation of nutritional assessments and interventions as part of oncology treatments and regimens.	**Theme 4: Weight loss measurements and management of UWL as recorded in the primary care records in a 12-month period** 97.1% of PACE study participants had ≥ 1 weight measurement in their notes in the past 12 months. Mean number of weight measurements was 2.94 in the past 12 months. Participants with significant documented weight loss had a mean number of weight measurements of 4.62 in the past 12 months. Most appointments where weight was recorded were with a nurse (primary care nurse – 32%, community nurse – 28.6% and specialist nurse – 14.3%)	**Theme: Help-seeking for UWL – barriers, enablers and responses from healthcare professionals** *Participants mentioned being weighed in routine disease reviews and having the opportunity to discuss weight loss. A few participants reported specifically mentioning weight loss in GP consultations.* *Healthcare professional response to weight loss* - *Positive reinforcement* *Role of healthcare professionals* - *Referral to specialist* - *Addressing loss of strength and function*	Silence across the three study stages Partial agreement across the quantitative and qualitative themes.

	53.4% of participants with significant documented weight loss had ≥ 1 management action in their notes in the past 12 months. Factors associated with a management action in the case notes in the past 12 months: - Care home residential setting - Increased frailty - Worse functional status - Decreased QoL scores - 'Underweight' and 'Normal' weight status - Loss of appetite to a severe or overwhelming extent in the previous week		

**Management action is a composite measure of one or more of the following in the case notes – assessment/investigation/referral/treatment.*

**QoL: quality of life

7.3 Summary

This chapter describes the results of the mixed methods phase of this PhD project. In this phase, the quantitative findings and qualitative themes were integrated to summarise the findings for each interview participant, map the patient delay pathway from the onset of UWL to the assessment and management of UWL and show convergence or silence using a convergence coding matrix.

The interview participants were younger (mean age 77.4 years vs 81.6 years) and weighed less than the PACE study participants (67.78 kg vs 76.49 kg). They were frailer than PACE study participants (mean Rockwood CFS of 5 vs 6) and had a higher mean number of comorbidities using the ACE-27 classification (4.93 vs 4.34). Nearly half the participants (n = 6/14) linked their weight loss to lengthy periods of hospitalisation or multiple hospital stays. All but one reported a loss of appetite in the past week and five participants had received some form of dietary supplementation and or a dietetic service referral.

Andersen's model of total patient delay was adapted and used to map the patient journey from the onset of UWL to the assessment or management of UWL in primary care. The adapted model compared well with the original model where the 'Appraisal' delay stage represented the majority of the delay. Unlike the original model, there was some overlap with the adapted model's delay stages.

A convergence coding matrix was used to integrate the findings from the quantitative and qualitative studies. The quantitative study findings and qualitative study themes were triangulated and examined for convergence. This generated five mixed methods research inferences or meta-themes: loss of appetite as an ambiguous indicator in primary care settings; perceived benefits of UWL and prioritisation of concerns, lack of concern about UWL and impact on help-seeking, role of family caregivers in reporting UWL and seeking healthcare interventions and healthcare professional role and clinical response when UWL is a concern.

The next chapter (Chapter 8) will provide a discussion of the findings from the study phases, strengths and limitations of the PhD study and recommendations for further research and some clinical implications.

8 Discussion and conclusions

8.1 Introduction

The aim of this mixed methods PhD study was to explore the experiences of older people and their caregivers who had lost weight unintentionally in the past 12 months. The study population was a cohort of patients attending an integrated care clinic (ICC), who were aged 65 or older and who were deemed to be at risk from moderate to severe frailty. These patients were recruited in 2019 for the Proactive Anticipatory Care Evaluation study (PACE study), which consisted of the recruitment of 300 participants who had been assessed by the ICC and a control group who had not received an ICC assessment. The PACE study was an evaluation of a new proactive frailty assessment clinic and a non-randomised matched control trial which assessed the impact of the intervention on care outcomes, especially the health-related quality of life, functional status, and symptoms. Of the 300 participants who received the intervention, 250 were recruited from the ICC and lived in private residences, and 50 were recruited from ICC clinics at care homes in the Hull region.

There were three sub-studies exploring chronic breathlessness, opioid pain medicines and unintentional weight loss (this PhD project) in this study population.

This patient cohort had a variety of chronic diseases and conditions that could have caused unintentional weight loss (UWL) linked to a condition such as cachexia. Exploring their experience of UWL in the past 12 months, therefore, would potentially describe cachexia risk or the beginning of a pre-cachexia phase. Additionally, data were gathered to describe the assessment and or management of UWL in primary care consultations in the previous 12 months.

The overarching aim of the thesis was addressed by the following objectives:

- To identify and describe the tools and methods used to screen for and assess the symptoms of cachexia, and in which health settings, as presented in the published literature.

- To determine the prevalence of UWL and loss of appetite in the last 12 months in older patients at risk of cachexia. These symptoms were used as a proxy for cachexia risk.
- Within a cohort of older patients at risk of moderate to severe frailty, describe the characteristics of those with UWL in the 12 months and compare their demographics, comorbid conditions, and functional status to those without UWL.
- To describe if and how primary healthcare professionals document weight measurements and the assessment of UWL in the clinical record.
- To elicit the views of those with UWL (and their caregivers) about their symptoms; their experiences of how their symptoms have been assessed and managed by healthcare professionals in primary care settings; and what advice or guidance they were given about this weight loss.

To meet the above objectives, I used four methodological approaches to answer 16 research questions. The PhD project was divided into four phases – a systematic review of the literature, a quantitative research phase, a qualitative research phase and a mixed methods research (data integration) phase.

In this chapter, I will discuss the key findings from the four study phases, summarised in Table 29. I will then discuss the extent to which the research questions for this PhD project have been answered, the implications of these findings and the strengths and limitations of this thesis.

8.2 Research questions and main findings of the study

8.2.1 Summary of main findings

The main findings of the study are displayed in Table 29.

Table 29: Research questions and the main findings of the study phases

Research questions	**Summary of findings**		
	Phase 1 Systematic literature review	**Phase 2** Quantitative study	**Phase 3** Qualitative study
1. What tools or methods are used to identify and assess cachexia symptoms and in which healthcare settings?	All 98 studies included in the narrative synthesis were conducted in secondary or tertiary care settings. Assessment tools: Weight measurements (97 studies) and self-reporting (1 study) BMI (74 studies) Body composition (68 studies) - Skinfold measurements - Bioimpedance analysis (BIA) - DXA scans, CT scans and MRI scans	In primary care settings: Documented assessments in case note records were mainly: – Weight measurements – Nutritional assessments – Assessment of appetite	Self-report and observation of symptoms by spouse/partner/ caregivers. Some interview participants reported that they expected to be weighed if UWL was reported to primary care professionals.

	Other assessments include physical function, physical activity, muscle strength, nutritional status, quality of life and systemic inflammation.		
Phase 2 Quantitative study			
The nature of self-reported UWL in older patients at risk of severe frailty			
2. What proportion of the participants self-reported UWL during the previous 12 months before attending an integrated care clinic?	24% of 300 study participants reported UWL in the previous year		
3. What are the characteristics of participants with self-reported UWL in the previous 12 months compared with those without?	Patients with self-reported UWL had a lower mean weight (65.51 kg vs 80.1 kg) compared to those without UWL and were significantly more likely to be underweight ($p<0.001$) or normal weight ($p = 0.002$). Participants with self-reported UWL were more affected by poor appetite – to a moderate ($p = 0.027$), severe and overwhelming extent ($p<0.001$) than participants without UWL.		
The nature of documented UWL in older patients at risk of severe frailty			
4. What proportion of the participants had documented UWL during the previous 12 months before attending an integrated care clinic?	24.5% of participants had significant weight loss (≥5%) documented in primary care records in the previous 12 months (range 2.5–26.70 kg).		

5. What are the characteristics of participants with documented UWL in the previous 12 months compared with those without?	Characteristics of participants with significant documented weight loss in the past 12 months were: the living in a care home setting, increased frailty, a lower BMI, poorer functional status and poor appetite in the past week to a severe and overwhelming extent.
6. What factors are associated with a documented UWL in the previous 12 months?	The factors possibly associated with a significant documented weight loss in the previous 12 months were frailty as measured by the Rockwood Clinical Scale and residing in the 2nd most deprived quintile in Hull.
Self-reported UWL and associations with documented UWL	
7. When participants report UWL in the previous 12 months, how many have unintentionally lost weight, as recorded in their primary care records?	Forty-two participants (29.6% or 42/142) had documented weight loss (any level) in the previous 12 months and correctly self-reported UWL Thirty-two participants (56.1% or 32/57) had significant documented weight loss (i.e., ≥5% weight loss) in the previous 12 months and correctly self-reported UWL.
8. What factors are associated with a self-report of UWL in the previous 12 months?	Factors possibly associated with a self-report of UWL included the following: living situation, documented weight loss, significant documented weight loss (≥5%) and loss of appetite in the previous week. Participants who lived in a care home setting were less likely to report UWL compared with those who lived alone.
Weight loss measurements and management of UWL were recorded in the primary care records of older patients at risk of severe frailty in the 12-month period before attending an integrated care clinic	
9. How often are older patients who have been assessed for frailty weighed in primary and community care settings, as documented by healthcare professionals, in the 12-month	Nearly all participants (97%) had one or more weight measurements documented in their case notes in the previous 12 months.

period before attending an integrated care clinic?	The mean number of weight measurements differed significantly between participants with and without documented weight loss ≥5%, 4.62 vs 2.40.
10. In what kinds of primary and community healthcare appointments are the weight measurements of these older patients routinely collected?	Most (75%) weight measurements were recorded in consultations with nursing staff, including primary care, community care and specialist nursing care. In primary care consultations, weight measurements were generally taken as part of regular disease reviews—for instance, respiratory, diabetic and cardiovascular reviews.
11. What assessments are used (or referrals made) for weight loss in these patients?	Assessment and management of documented weight loss—119 investigations, assessments and treatments were recorded in the primary care records of 237 PACE study participants in the previous 12 months. - Nutritional assessments - Further referrals - Faecal Immunochemical Test - Amend diabetes treatment - Assessment of appetite - Blood tests and scans/x-rays - Supplements / fortified diet - Enteral feeding
12. What proportion of these patients are further investigated for the cause of their weight loss in the 12-months before attending an integrated care clinic?	The proportion of participants with documented significant weight loss (≥5%) with a management action was 53.4% (n = 31/58).
13. What are the characteristics of patients who had a management action* for their UWL in the previous 12 months compared with those without?	Characteristics of participants who had a management action for significant weight loss in the previous 12 months:

	Living in a care home setting, increased frailty, poorer functional status, worse QoL scores and poorer appetite in the past week.
14. What factors are associated with the management* of UWL, as documented in the primary care records of older patients, in the 12 months before attending an integrated care clinic for frailty management? (*assessment/investigation/referral/treatment)	Patients with documented weight loss in their notes who received a management action had a mean weight difference of 16.83 kg and were more likely to be underweight or normal weight compared to those without a management action. Patients with significant documented weight loss were less likely to have a management action recorded in their notes if they lived alone, and if they were overweight, obese and severely obese. Factors possibly associated with a patient having a management action in their notes included functional status (AKPS), heaviest weight documented in the previous year, and loss of appetite in the previous week (IPOS: Loss of appetite score).
Phase 3 Qualitative study	
15. What are the experiences of patients (and caregivers') with UWL of their symptoms and the assessment and management of their symptoms in primary care?	Six qualitative themes: Experiences and perceptions of appetite loss associated with UWL Normalisation and rationalisation of appetite loss by most participants Impact of health and functional status and health literacy Experiences and perceptions of UWL Witness and advocacy roles of family caregivers Help-seeking for UWL: barriers, enablers and responses from healthcare professionals

Phase 4: Integration of findings	
16. How is UWL assessed and managed in primary care, and how is it experienced by older patients who might be at risk of developing cachexia?	Five meta-themes: Loss of appetite as an ambiguous indicator in primary care settings Perceived benefits of UWL and prioritisation of concerns Lack of concern about UWL and its impact on help-seeking Role of family caregivers in reporting UWL and seeking healthcare intervention Healthcare professional role and clinical response when UWL is a concern

8.2.2 Addressing cachexia risk and pre-cachexia in primary care

Three significant factors led to a change in focus for the questionnaire. The term 'cachexia' was removed, as it was felt that participants would be unfamiliar with it and making enquiries about the term (either online or with healthcare professionals) would cause concern for participants and family caregivers. Additionally, the results of the systematic review confirmed the need for a shift in focus, as the ICC spanned primary/secondary and community settings and measurements for cachexia symptoms were not routinely included in the patient assessment. Few participants attended the ICC with a diagnosis of cachexia, even if they were at risk of developing it or in cases where it was clinically evident. Therefore, instead of enquiring about cachexia, the focus was on the main symptoms of cachexia, such as UWL and loss of appetite. The baseline questionnaire was amended to reflect this change in focus (see Appendix 1).

Cachexia studies and diagnostic criteria have described and incorporated a pre-cachexia stage in their assessment of patient symptoms (9, 10). Only a small proportion of the studies identified in the systematic literature review described the assessment of pre-cachexia or the risk of developing cachexia. These studies were all conducted in secondary care settings rather than primary care settings. UWL, as the main symptom of cachexia, can be an early sign that indicates an underlying disease or a worsening of chronic illness. Therefore, this symptom could potentially be investigated in non-specialist care or lead to a referral to and further investigation in secondary care. UWL in older age patients can be caused by a number of factors. The majority of participants in the PACE study who had experienced UWL in the previous 12-months did not have their weight loss investigated for underlying causes, and in some cases, the weight loss was attributed to an acute event or trigger and thus viewed as temporary.

The second symptom of cachexia that was often assessed as part of a diagnostic criteria, was loss of appetite. Loss of appetite was commonly assessed in PACE study participants as part of routine nutritional screening whether they had lost weight or not. UWL and loss of appetite will always need to be assessed and further

investigated when deemed to be clinically appropriate. However, an additional complexity is that these two symptoms are commonly experienced by older patients with chronic conditions and end-stage disease, so the initial stages of cachexia can easily be overlooked in primary care settings. The normalisation of loss of appetite may lead to patients and healthcare professionals only recognising that there is a problem when there is an accompanying weight loss that is classed as significant. The systematic review identified few studies in the area of pre-cachexia and this is perhaps to be expected in secondary care settings. The focus in non-specialist care settings may need to be placed on the *risk* of developing cachexia rather than on UWL as a component of a pre-cachexia phase. Pre-cachexia was not a fully accepted concept in cachexia research studies in the immediate years after the consensus diagnostic criteria by Fearon (9). However, research studies, as identified in the systematic review, are increasingly reporting assessments of cancer-related cachexia that include a pre-cachexia stage (249, 311, 369). In these studies, pre-cachexia was identified when patients were admitted to secondary/tertiary health care settings for further treatment or when pre-treatment weight loss was retrospectively assessed. The intention for identifying this stage is to apply multi-modal treatment options for weight loss as soon as is possible as degrees of weight loss and cachexia risk is being linked to survival outcome for cancer patients (369). Additionally, if cachexia can be identified at earlier stages, inflammation is less impactful and nutritional supplementation may have an increased possibility of being effective. There perhaps needs to be a different approach used in primary healthcare settings where healthcare professionals are educated to associate UWL with the *risk* of developing cachexia amongst other possible diagnoses. Linking UWL to cachexia and other muscle depleting conditions such as sarcopenia, at an earlier stage, may lead to identifying possible causative factors much sooner.

8.2.3 Significance of UWL as a symptom

A quarter of the PACE study participants reported UWL in the previous year. The case note review revealed that a similar proportion of participants (24.5%) had significantly documented weight loss (≥5%) in the past year. These findings are

consistent with those of other studies that reported prevalence rates of UWL in older people between 15–20% (398-400), increasing to 27% in older people with frailty (401). In this study, the prevalence of UWL was reported in a study population where most of the participants (69.9%) were classified as overweight, obese or severely obese. Recent UWL in a comorbid older patient population has a cumulative impact on patient outcomes, even when patients are overweight and obese (402). This is especially a concern in this older study population, as they are at risk of malnutrition and frailty. The case note reviews showed that assessments for malnutrition and appetite loss were routinely conducted in community nursing and in some primary care nursing consultations. However, 'malnutrition' in this thesis refers to undernutrition; there is a risk to health with overnutrition in overweight and obese patients. This study clearly demonstrated that unexplained weight loss was sometimes more readily disregarded by those who were overweight or obese. This may be a crucial factor in identifying and responding to this symptom.

Both states of extreme weight loss and weight gain carry similar risks to health. The European Association for Predictive, Preventive and Personalised Medicine (EPMA) compared anorexic and obese body phenotypes and called this the *'paradox of the similarity of health risks'* (403). The comparison of the two phenotypes showed that both had increased risks of cardiovascular disorders, chronic inflammation, poor wound healing and an increased predisposition to cancer with poorer outcomes.

Recent UWL may be regarded as an additional health event that represents an acute state of malnutrition, and being overweight and obese does not reduce this impact on hospital mortality and outcomes (402), as previously described in Chapter 2. This is of significance to the PACE study population due to the high proportion of overweight and obesity.

8.2.4 Weight measurements in primary care

In this study, at least one weight measurement was recorded in the majority of participants' notes in the previous 12 months. This is to be expected in this patient population, which was comprised of older patients (≥65 years of age) with a risk of moderate to severe frailty. In routine primary care practice, however, weight measurements of adults may be less common. Longitudinal analysis of UK primary care electronic health records showed that one-third of adults over forty had a weight measurement recorded annually (404). In Nicholson and colleagues' investigation of just under 5 million patient records, the characteristics independently associated with an increased likelihood of weight recording were female sex, younger and older adults, low or high BMI, increased deprivation, a greater number of comorbidities and more frequent consultations (404). Of interest is the association between the likelihood of weight measurements and low and high BMIs. Weight measurements in patients with a low BMI could be the result of routine appointments, such as chronic disease reviews or monitoring, because of a nutritional deficit or a weight loss-related issue. Weight measurements in patients with a high BMI are also linked to routine chronic disease reviews and, more commonly, opportunistic measurements. For some time periods, weight measurements of patients with a high BMI were incentivised in NHS primary care in relation to existing disease (e.g. as part of the Quality and Outcomes Framework) or in preventative health screening programmes (e.g. NHS Health Checks) (404). Some PACE study participants with UWL may have previously been accustomed to being weighed in primary care consultations due to obesity-related conditions. Unintentional weight loss, therefore, may not initially be a concern.

8.2.5 Concern about UWL and help-seeking

The authors of the Andersen model of total patient delay reported that appraisal delay constituted the majority (at least 60%) of the total delay from the onset of an unexplained symptom to the diagnosis and treatment of cancer (204). In adapting this model, it became apparent that the appraisal and processing of UWL as a symptom overlapped with identifying it as a problem, as shown in Figure 7. In the

original model, the authors state that the delay stages are independent. This was not the case with this adaptation as the processing and appraisal of UWL as a symptom includes the normalisation of loss of appetite and weight loss. Additionally, participants' rationalisations for possible causes (e.g. polypharmacy, post-hospitalisation, changes in diet) and their perception of the positive benefits of weight loss, and the response of healthcare professionals to their weight loss led to a complex appraisal stage. This multilevel and overlapping appraisal stage causes delays in identifying weight loss as a problem, which contributes to delays in help-seeking.

'Lack of concern' was among the themes identified in the qualitative interview data. The lack of concern that some participants expressed about their weight loss could be explained by the adapted model and the interaction of the factors mentioned in the adapted Andersen model. Several influential factors possibly contribute to this theme, including the positive responses from healthcare professionals to weight loss, previous routine weight measurements as part of chronic disease reviews where weight loss is encouraged and the public health messages that participants may have previously received about the positive benefits of weight loss. Previous studies have described the challenges of delivering brief interventions for obesity in primary care (405), so it is perhaps not surprising that healthcare professionals respond positively to observed weight loss when a patient attends a routine appointment.

The findings from the qualitative data analysis demonstrate the barriers to patients appraising their symptoms and being concerned. Prado and colleagues reported that malnourished patients may describe their nutrition status as good to excellent despite their poor status (139). This could be due to a number of factors – a misunderstanding of what constitutes a healthy body or a healthy self-image, an association of UWL as a perceived positive benefit, or a denial of reduced dietary intake or UWL to maintain a positive effect (139). Some of the findings in this PhD study support this evidence in that the perceived positive benefits and effects of UWL were remarked upon in the qualitative interviews. Patients who perceived

the UWL as a positive were either overweight or obese initially, had previously attempted to lose weight intentionally or had improved their health in some way, for instance, minimising the need for diabetic medication. It was a challenge, therefore, to assess the causative relationship between the reactions of healthcare professionals and the thought processes that led to the rationalisations and the perceptions of positive benefits. Were participants not concerned about their UWL because healthcare professionals had reassured them? Or were they generally not concerned about their UWL and then minimised it in primary care appointments?

There were additional factors related to the timing of study recruitment that could also contribute to why patients were not concerned by their symptoms. I met and interviewed study participants at various stages of their weight loss. Some participants had experienced UWL over a number of years and may have had initial concerns when the weight loss commenced. The abatement of this initial concern could have been due to acceptance of a new body image, positive responses to the weight loss, as mentioned above, and the rationalisation of the perceived benefits of weight loss rather than weight gain. Furthermore, initial assessments or investigations for the UWL might have reassured participants that there were no serious underlying causes. I would not necessarily have noticed what was done in this immediate timeframe to address UWL, as the case note review focused on primary healthcare interactions in the previous 12 months.

Participants stated in their interviews the factors that would make them concerned about UWL (rapid and severe weight loss for no obvious reason) and what factors would drive help-seeking behaviours (unresolved weight loss and concern from family or loved ones). When participants and their caregivers sought medical advice, they expressed concern due to their perceptions of the severity of the weight loss and their concern about underlying causes. Caregivers and loved ones also expressed concern about how the loss of appetite had affected the participants' daily dietary intake and how it had changed their normal routines. This was reflected in the literature, specifically for cancer-related cachexia. Reid and colleagues have described the anxiety and conflict that can arise at mealtimes when

patients with cachexia are unable to eat when they are visibly underweight and need nourishment (151). The results of the qualitative phase showed that caregivers were the observers of the changes in appetite and resulting weight loss, and they were likely to be more dependable narrators in healthcare consultations. The concern and worry expressed by family caregivers and the wider family were motivating factors in pursuing medical intervention and further investigation to address the UWL.

8.2.6 Role of sarcopenia or muscle wasting in UWL

While sarcopenia is distinct from cachexia, both can be associated with inflammatory changes caused by chronic and end-stage disease (406), and sarcopenia has been incorporated into diagnostic frameworks for cachexia since 2011 (9). The Fearon criteria for cancer-related cachexia are either a weight loss > 5% in the past six months, a weight loss of 2% or more in those with a BMI of < 20 kg/m^2, or a weight loss of 2% or more in those with sarcopenia (9). There is, therefore, some overlap between the two syndromes when investigating UWL in comorbid patient populations.

Themes identified in the mixed methods study include 'lack of concern' or a 'prioritisation of concern'. Although some participants expressed minimal concern for the UWL, as described in the previous section, they were more worried about the effects of weight loss. Participants mentioned a 'loss of strength' or 'weakness' with the weight loss and how this had impacted their ability to conduct their regular activities. They were more easily fatigued and expressed frustration about how this affected their lives. In the qualitative interviews, participants were asked about their ICC assessment and what they had learnt from it. A few participants reported how valuable they found the physiotherapy assessment, stating that they were given suggestions on how to increase their levels of physical activity and mobilise more easily. These participants mentioned that they were either looking to access more physiotherapy through their GP or wondered how they could return to the ICC to access more input. The interview participants recruited had a number of mobility issues, and those who had lost significant amounts of weight were

incredibly limited in even moving around their homes. The level of integrated care received through their multidisciplinary assessment was rare for most participants and highlighted what was missing from their care. Those who had returned home from lengthy hospital stays and had experienced UWL were still physically weak. They may have received input from the dietetic service or their GP with respect to dietary supplementation, but they reported a need for some sort of physical rehabilitation to allow them to regain their strength and some of their mobility. Certainly, this is a resource-challenged area of primary and community care, but it was evident that the ICC had exposed the participants to another aspect of care that they realised would be valuable.

Sarcopenia, as a condition, was rarely mentioned in primary care case notes and is not a term that patients would readily know. As Avgerinou (2020) stated, *'a diagnosis of sarcopenia is very rarely made or documented in medical records; despite being a clinical entity*' (111); however, it became evident from the qualitative interviews that participants were mainly describing the effects of muscle loss. When discussing muscle weakness, some people pointed to their arms to demonstrate the loss of muscle mass.

The challenge for primary care healthcare professionals in identifying sarcopenia as a clinical entity is that the main symptom of UWL is also present in malnutrition, frailty, and cachexia. The four conditions can overlap and have a synergistic relationship (407). An investigation of the total UK Biobank population (111, 983 people) revealed that 45.0% had frailty, 5.8% had sarcopenia, 0.1% had malnutrition and 0.04% had cachexia (408). However, this Biobank population had a mean age range of 55 to 61 years, so the prevalence of these four conditions would be higher in an older population. The most prevalent syndrome among 100 hospitalised older patients (≥70 years) was sarcopenia (42%), followed by frailty (33%), cachexia (32%) and malnutrition (15%), according to a previous study (140). This contradicts findings from the case note review, where a common management action to address UWL in primary care was using nutritional screening tools and interventions to identify and treat malnutrition in this patient group.

8.2.7 UWL in the overweight and obese

In this study, participants who were overweight or obese were less likely to report UWL, less likely to have documented weight loss in their notes and less likely to have a management action to address their documented weight loss. This is reflected in the adapted Andersen patient delay pathway, which shows how the perceptions of patients and healthcare professionals lead to delays in recognising UWL as a problem. The impact of obesity on this delay cannot be overstated.

Participants in the study who were overweight or obese reported that they had attempted to lose weight in the past and were conflicted about seeking help if weight loss had always been perceived as beneficial to their health. The pervading view that weight loss is preferential to being overweight or obese has been explored in other studies (409). Participants also reported reluctance to regain weight, which would delay help-seeking behaviours and impact compliance with recommended nutritional interventions The majority of study participants were female, and as a result of the stigma associated with being categorised as overweight or obese, women already avoid healthcare consultations due to stressors that may or may not be related to their weight (410).

The extent of cachexia in a patient can be underestimated and missed in the early stages if the patient is obese (37). This is also the case for UWL in a primary care setting. It has been proposed that healthcare professionals underestimate patients' weight when using visual appearance (411) and this might be due, in part, to a change to what is now considered a 'normal' body size (412-414). Any initial weight loss may not be immediately noticeable. However, weight loss caused by cachexia and sarcopenia is due to loss of muscle mass and fat mass (in cachexia), which needs to be acknowledged by healthcare professionals.

There were interview participants who described their experiences of UWL as losing muscle mass while being overweight or obese. In the literature, this condition is referred to as sarcopenic obesity, and it is increasingly common in

adult populations, where the prevalence of overweight and obesity is also rising. However, accurate estimates of the prevalence of sarcopenic obesity are limited due to a lack of a universally adopted definition of sarcopenia, the use of various assessment techniques for body composition and a lack of consensus for suitable cut-off points for obesity (415). The significance of sarcopenia obesity is its deleterious effect on physical function and chronic disease processes. It has been postulated that sarcopenic obesity has a greater impact on metabolic disorders, cardiovascular disease, and mortality than either obesity or sarcopenia due to the synergistic effect of both conditions (415, 416). The qualitative findings demonstrate that the participants' experiences with muscle weakness may represent a rising trend of sarcopenia and sarcopenic obesity that will need to be addressed in all care settings.

8.3 Strengths of the study

This study represents a positive initial step in exploring how UWL is possibly linked to the early stages of cachexia present in patients who are most at risk. Research has been previously conducted to describe cachexia's pathophysiology and identify possible nutritional and pharmacological interventions. The pre-cachexia phase, as described by Muscaritoli (2009) and Fearon (2011), is of importance as it represents clinicians' and researchers' efforts to describe the early developmental phases of this complex syndrome. They argued that addressing how this early phase can be identified will lead to opportunities for early intervention. Cachexia will then become a potentially treatable syndrome, rather than an inevitable marker of advanced and end-stage disease.

There have been few qualitative or mixed methods research studies on cachexia and even fewer on pre-cachexia. Most studies, as evidenced by the systematic literature review in Chapter 4, are cancer cachexia studies and all were based in secondary care settings. This study attempts to link UWL in a primary care setting to cachexia in this older comorbid population. As these patients were at risk of moderate to severe frailty and had a number of chronic conditions (and therefore

chronic inflammation), it meant that the experience of UWL which could possibly be linked to cachexia could be explored. Using a mixed method research approach meant that quantitative data could describe UWL in this population, while qualitative data could help to explain the quantitative data in greater depth.

UWL has several causative factors, so it is challenging to distinguish weight loss, which is a possible symptom of early cachexia, from other causes. However, this is the reality that healthcare professionals in primary care face, so an exploration of this study population's experiences with UWL is ideally placed in a primary care setting. Ideally, both perspectives (patients and healthcare professionals) would have been explored in this PhD study as originally planned. What is important to note, though, is that this study focuses on the 'patient voice' on this rarely researched issue. What is even rarer is the prioritisation of the patient's voice from an older patient population at risk of severe frailty.

This was an efficient and streamlined research project in which a small research team conducted the recruitment. The main study was a service evaluation in the form of a non-randomised matched control trial with three PhD sub-studies using mixed method approaches. Recruiting participants at the ICC provided this PhD researcher with a unique opportunity to recruit patients with moderate to severe frailty and, as a result, a number of chronic conditions linked to UWL and possible cachexia. The patients were referred by their GPs from practices across the Hull CCG region and were broadly representative of the patient demographics in this age group. From a practical perspective, the research team did not, therefore, need to approach individual GP practices and was still able to recruit primary care patients, despite being in a non-primary care setting.

The ICC in the relatively new 'integrated care' space represents an interface between primary and secondary care. Using multidisciplinary assessments, the service aims to proactively coordinate care in primary and secondary care settings to prevent frailty deterioration that leads to chronic disease exacerbations, hospital admissions and poorer health outcomes. With respect to this PhD study, the

impact or context of the integrated care setting was limited, as most of the focus was on primary care. The case note review and qualitative interview data showed that the ICC was considered a secondary care setting in which a few interview participants were referred for a global assessment that could investigate aspects of their weight loss, amongst other things.

8.4 Impact of COVID-19 on this PhD project

Both quantitative and qualitative data collection were disrupted by COVID-19 pandemic lockdowns and national stay-at-home orders. In common with most healthcare settings, the Integrated Care Clinic closed in March 2020 to non-essential research.

The closure of the ICC meant that I could not access SystmOne, the electronic health record system, which I was using to conduct the secondary case note review for details of weight measurements and details of the healthcare appointments where weight was recorded. I was fortunate to be granted permission to access the ICC for five days in late September 2020 to complete as much of the case note review. Unfortunately, some case notes were inaccessible due to participants dying or moving practices in the intervening six months. Additionally, the major denominator I hoped to use in the analysis was not collected. This was the total number of healthcare appointments each patient had in the 12 months before their ICC assessment, irrespective of the weight being recorded. This was too time-consuming to collect in the time allotted, so I concentrated on reviewing all the case notes I could access for weight measurement information.

In terms of the qualitative interviews, it was already challenging to recruit healthcare professionals to participate, and by March 2020, I had recruited four healthcare professionals and conducted two interviews out of ten that had been planned. A decision was made to pause recruitment of healthcare professionals at the end of 2019 and then it was ceased in 2020 due to restrictions on non-essential research being conducted. This was especially appropriate because of the types of

healthcare professionals I wished to recruit, such as GPs, practice nurses and care home assistants, were heavily involved with the pandemic response.

The absence of qualitative interview data from healthcare professionals' perspectives severely limited my ability to explore their perceptions and views of UWL and how they respond to it. The gap created by these missing perspectives was evident in my examination of the patient delay and treatment delay pathways using the Andersen model (49) (Figure 7). I used the qualitative data, which mentioned healthcare and healthcare professionals and aspects of the quantitative data that documented the clinical response to UWL. Undoubtedly, integrating interview data from healthcare professionals would have provided additional information regarding the delays encountered when assessing and managing patients with UWL. Their perspectives on managing symptoms such as UWL in older patients with a number of comorbid conditions and systemic challenges would have been valuable. Other limitations are discussed in the next section.

8.5 Limitations of the study

Referrals to the ICC were meant for primary care patients who were classified as being at risk of severe frailty (with an electronic Frailty Index (eFI) score ≥ 0.36). When the research team conducted the baseline case note review, we found that the patient population was more heterogeneous regarding frailty risk and comorbidity. Twenty percent of the eFI scores were missing, just over 50% of study participants were classified as having a severe risk of frailty and 16% were categorised as having a moderate risk. Of interest, nearly all participants had a Rockwood Clinical Frailty Scale score calculated to categorise their actual frailty at the time of the appointment, and most were categorised as being mildly (score of 5) and moderately frail (score of 6). This more heterogeneous sample was partly why recruiting participants who had entered an established cachexia phase was challenging. These patients were often too unwell to attend the clinic, and those in attendance prioritised the clinical assessments and were not amenable to being recruited. One participant recruited with severe muscle wasting cancelled her

interview, quite rightly, because of a deterioration in her health. A patient cohort who were classed as having moderate risk of frailty were therefore more physically robust and would show early signs of UWL which is partly why I changed the focus of my research. The heterogeneity encountered through the primary care referrals and the high proportion of missing eFI scores would also impact the generalisability and transferability of the research findings in a similar way. There would be inherent limitations in using the findings to fully examine cachexia in the primary care and community setting.

The majority of primary care practices in the Kingston upon Hull CCG area were able to refer patients to the ICC, so the demographics of patients attending were broadly representative of the Hull population – 93% White. In the 2011 UK census, however, the two main white ethnic groups were White Caucasian (89.7%) and Other White (4.1%). Hull has a white non-British population, and they appear to be unrepresented in this study population. It is unclear if this is because they did not engage as much with the primary care system as the white British group, or if this is due to the poor sensitivity of the ethnicity data categories that were employed for the PACE study. It could be a combination of both of the above factors or because the majority of the white non-British population in Hull is of working age and would not meet the age requirements for the PACE study, even if they were referred to the ICC.

The focus of the data collection at baseline for the PACE study had to include a wide range of survey questions. These questions encompassed the baseline status of the participants and needed to include three sets of screening surveys for the PhD sub-studies. For this reason, my screening survey questions were somewhat limited, and the participants were not asked for possible reasons for their UWL. While this was something that was elicited as part of the qualitative interview process, I feel that not having this information hindered the recruitment process for the qualitative interviews. Participants did not want a 'follow-up interview' concentrating on weight loss because they felt that the weight loss was temporary

and or resolved. I would have changed my approach slightly to ensure that participants were comfortable sharing their experiences of resolved UWL.

There are limitations in how objectives can be met and research questions answered by the use of case note review data. Limitations of the case note review as a data collection method have already been described in Chapter 3. Fortunately, these limitations can be minimised through the use of mixed methods research data. Mixed methods research enables a researcher to complement and elucidate each research phase by collecting and analysing different types of data.

What became apparent when conducting the case note review was that the case notes represented how healthcare professionals recorded the assessments. It was challenging to distinguish between how they 'assess and monitor' weight loss and how they 'document' the monitoring of weight loss. The presence of a weight recorded in the notes was not always a sign that the patient had been weighed in that consultation. The weight measurement could be taken from a recent appointment, or the healthcare professional could ask the patient for their weight and record it. As part of the case note review, the appointment types and the healthcare professionals with whom the appointment was made were categorised. It was assumed that the healthcare professional who recorded the weight at that appointment also took the weight measurement. However, the records in an electronic healthcare record system were limited in this respect. For instance, the appointment could be with a GP, but the weight measurement could be taken by a healthcare assistant or practice nurse.

The intentionality of weight loss is not always clear from electronic health records. Therefore, the documented weight loss in this study could include some participants with intentional weight loss. To mediate for this, significant documented weight loss (those who have lost ≥5% of their weight) was used as a proxy for UWL. Using significant weight loss instead of any documented weight loss excludes those who have weight fluctuations for a number of reasons, for example, the small number of participants with heart failure on diuretics. This

approach also excluded the weight fluctuations experienced by patients with larger BMIs who may have been trying to lose weight and had not disclosed this to the research team at the time of recruitment.

Delays in the project, as described in the previous chapter section, meant that healthcare professionals were not recruited for the qualitative phase of this project. I originally sought to recruit a balance of general practitioners, care home care assistants and other allied health professionals. Consequently, there were no accounts of the practice of weight measurements in primary and community care from the perspectives of healthcare professionals. What was witnessed in the ICC at the time of the assessment was that most patients were weighed, but on occasion, patients who were not weight bearing could not be weighed. One wonders the impact these kinds of mobility issues would have in primary care settings, where patients are being weighed more regularly. This would have been something to follow up on in interviews with healthcare professionals. I also wanted to explore with healthcare professionals their knowledge and familiarity with muscle wasting and the terms 'sarcopenia' and 'cachexia'.

There is often a balance required when analysing data collected for another purpose, and while the opportunity to use the PACE study population was a pragmatic decision, there were some implications for the quantitative analysis. The sample size was not optimal for some of the predictor variables entered into the logistic regression models. The rules of thumb for minimum sample sizes for multiple regression analyses vary greatly in the literature. However, as the analyses were conducted to assess associations and were more hypothesis-generating than hypothesis-testing, the results of the quantitative analysis should be seen as valuable for future research in this area.

8.6 Implications for clinical practice

Weight measurements and nutritional assessments are routinely conducted in primary care settings for older patients, especially if they receive frequent reviews

for chronic conditions such as COPD or type 2 diabetes. Loss of appetite was also assessed (and documented) in primary care consultations, and participants with UWL reported moderate to severe appetite loss. However, loss of appetite was often dismissed by participants, and this PhD lacked qualitative data from a healthcare perspective which would have explored healthcare professionals' views on how the assessment and overall management of loss of appetite was handled in primary care settings. Most documented clinical responses addressed UWL rather than loss of appetite.

Common interventions for managing UWL in this study ranged from repeated weight measurements, nutritional interventions, investigating the cause of the UWL and managing the underlying condition and symptoms. What may be missing from these interventions is the effective management of the impact of muscle loss and the loss of strength. This was demonstrated in how the PACE study participants valued the physiotherapy and occupational therapy input, which addressed their loss of strength and function. A focus on the loss of muscle mass (i.e. sarcopenia), especially in older overweight or obese patients, is needed as this population increases. At present, many of the methods used to assess sarcopenia are used in investigational or research settings but are not applied in clinical practice (417). There is scope to add simple measurements of muscle strength, such as handgrip strength, using a dynamotor to assess muscle loss, either routinely with weight measurements or as part of the assessment of UWL in at-risk populations.

In the majority of cases, weight loss should be encouraged in patient populations with chronic conditions who are overweight or obese. Depending on their comorbidities, intentional weight loss has the potential to improve symptoms, reduce levels of pain and improve mobility. However, there needs to be increased awareness of the impact of sudden unintentional weight loss in older patients at risk of frailty. Weight loss is not always beneficial, and in this patient group, unintentional weight loss may represent an underlying problem. What might be regarded as a positive development by patients and healthcare professionals may

lead to delays in reporting and recognition of the underlying problem, which precedes worsening frailty and poorer health outcomes.

The increase in the older patient population living with multimorbidity will be associated with an increase in the inflammatory-based causes of UWL. Although cachexia studies and diagnostic criteria are predominately used in cancer and palliative care settings, there is increasing awareness of the non-cancer causes of cachexia. Chronic conditions such as chronic heart failure, COPD, chronic kidney disease and rheumatoid arthritis can also cause cachexia. As reported in the systematic review, studies of the non-cancer cause of cachexia were also based in secondary or specialist care settings. In the near future, there will be implications for how cachexia related to chronic conditions is assessed and managed in primary care settings where these conditions are most frequently managed and reviewed.

8.7 Recommendations for future research and practical applications

The qualitative data highlight the importance of eliciting the experiences and views of healthcare professionals regarding their experiences in assessing and managing UWL. In particular, ascertaining the times when healthcare professionals feel it is appropriate to reassure patients and their caregivers and when they would investigate the underlying causes of UWL. It would be valuable to determine from healthcare professionals, their threshold for initiating investigations for UWL and if any of their actions included safeguarding mechanisms for asking the patients to return for a review if weight loss continues, is impactful or sustained.

Further work could be undertaken with healthcare professionals to explore their perceptions of weight loss in this patient group and any perceived positive and negative benefits and how that is communicated to patients. Additionally, work could be conducted to explore healthcare professionals' knowledge of some of the inflammatory causes of UWL, such as cachexia, sarcopenia and sarcopenic obesity. It would be important to examine their views of the type of patients in which they

see these conditions and what they feel their role is in the identification, assessment and management of UWL in a primary care setting.

The input of primary care healthcare professionals would be valuable in developing a primary care intervention to screen for and address the loss of appetite in high-risk patients. The intervention could be integrated into annual disease reviews and routine appointments and could be used to identify patients who are experiencing loss of appetite plus unintentional weight loss. There would be a potential to intervene where appropriate with nutrition interventions and physiotherapy.

In terms of research with patients and caregivers, there is potential to further explore the experience of UWL in older patients who are overweight and obese and to concentrate on eliciting views about how they rationalise intentional and unintentional weight loss and how the messages they receive during healthcare interactions impacts their views on weight loss. There is also potential to use qualitative research methods to better understand the normalisation of age-related loss of appetite and weight loss, how this leads to a delay in seeking healthcare and how it may also mask disordered eating in those with a previous history of eating disorders.

8.8 Summary of the thesis

This PhD project was undertaken to gain a better understanding of how unintentional weight loss, possibly associated with cachexia, in older patients at risk of severe frailty was assessed and managed in primary care settings. Quantitative methods were used to describe the patient population and examine the nature of unintentional weight loss and how it was managed, as documented in case notes. Qualitative methods were used to explore the views and experiences of older patients who had lost weight unintentionally in the previous 12 months. This is one of the first attempts to do this in this patient group and in this care setting using a mixed methods approach where quantitative and qualitative datasets were integrated.

This study has found that generally older patients at risk of severe frailty were weighed and monitored regularly in primary care settings. Almost all of the study participants had one or more weight measurements recorded in their case notes in the previous year. In this older patient population, appetite loss was normalised and rationalised by some as being a normal part of ageing. Participants expressed minimal concern about their unintentional weight loss if it was sustained and more concern was expressed about muscle weakness and changes to their appearance. However, participants reported that they would seek medical intervention if the unintentional weight loss was rapid, severe and with no obvious cause, as this could possibly be due to a malignancy. When patient and diagnostic delay stages were examined, it was evident that the appraisal delay stage, which represents the time taken to recognise unintentional weight loss as a problem, was complex and was influenced by health literacy, linking weight loss to polypharmacy, ageing, changes to dietary habits and chronic conditions.

The findings suggest that a lack of concern from both patient and healthcare professional perspectives impacted help-seeking behaviour and clinical responses to unintentional weight loss. This was especially evident when weight loss was not obvious, where it was deemed to be temporary or perceived to be beneficial.
The concern expressed by family caregivers was often the main driver for patients reporting unintentional weight loss and living with a spouse or partner increased the likelihood of a clinical response. Those who were overweight or obese were less likely to have a clinical response to the unintentional weight loss documented in the notes.

Unintentional weight loss in this care setting could be due to a number of causes. The findings indicate that weight monitoring and nutritional interventions in primary care predominantly targeted malnutrition. Cachexia was rarely mentioned, and sarcopenia and sarcopenic obesity may be the most neglected causes of unintentional weight loss in this patient population. An implication of these findings is that clinical responses to unintentional weight loss in primary care

need to be more proactive, lead to earlier interventions and need to be alert to overweight and obese patients in whom the impact of unintentional weight loss may be hidden.

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Appendices

Appendix 1: Baseline PACE study questionnaire with screening questions

PACE

Proactive Anticipatory Care Evaluation

Name _____

Date _____

The Information sheet will be read to you again to ensure you understand everything about the study and answer any questions you might have.

Your answers will be kept confidential and seen only by the research team

If you have any queries, please contact the study

Dr Mabel Okoeki (Project Lead)

Telephone: (01482) 463728

Email: PACE@hyms.ac.uk

SECTION ONE

ABOUT YOUR WELLBEING (IPOS)

Q1. What have been your main health problems or concerns over the past week?

.....

.....

.....

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick one box that best describes how it has affected you over the past week.

	Not at all	Slightly	Moderately	Severely	Over-whelmingly
Pain	0☐	1☐	2☐	3☐	4☐
Shortness of breath	0☐	1☐	2☐	3☐	4☐
Weakness or lack of energy	0☐	1☐	2☐	3☐	4☐
Nausea (feeling like you are going to be sick)	0☐	1☐	2☐	3☐	4☐
Vomiting (being sick)	0☐	1☐	2☐	3☐	4☐
Poor appetite	0☐	1☐	2☐	3☐	4☐
Constipation	0☐	1☐	2☐	3☐	4☐
Sore or dry mouth	0☐	1☐	2☐	3☐	4☐
Drowsiness	0☐	1☐	2☐	3☐	4☐
Poor mobility	0☐	1☐	2☐	3☐	4☐
Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week.					
_____	0☐	1☐	2☐	3☐	4☐
_____	0☐	1☐	2☐	3☐	4☐
_____	0☐	1☐	2☐	3☐	4☐

Over the past week:

	Not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Always*
Q3. Have you been feeling anxious or worried about your illness or treatment?	0☐	1☐	2☐	3☐	4☐
Q4. Have any of your family or friends been anxious or worried about you?	0☐	1☐	2☐	3☐	4☐
Q5. Have you been feeling depressed?	0☐	1☐	2☐	3☐	4☐
	Always	*Most of the time*	*Sometimes*	*Ocassionally*	*Not at all*
Q6. Have you felt settled or comfortable?	0☐	1☐	2☐	3☐	4☐
Q7. Have you been able to share how you are feeling with your family or friends as much as you wanted?	0☐	1☐	2☐	3☐	4☐
Q8. Have you been given as much information as you needed?	0☐	1☐	2☐	3☐	4☐
	Problems addressed/ No problems	*Problems mostly addressed*	*Problems partly addressed*	*Problems hardly addressed*	*Problems not addressed*
Q9. Have any practical problems resulting from your illness been addressed? (such as financial or personal)	0☐	1☐	2☐	3☐	4☐
	On my own	*With help from a friend or relative*			*With help from a member of staff/researcher*
Q10. How did you complete this questionnaire?	☐		☐		☐

SECTION TWO HEALTH QUESTIONNAIRE (EQ-5D-5L)	
Under each heading, please tick the ONE box that best describe your health TODAY	
MOBILITY	
I have no problems in walking about	☐
I have slight problems in walking about	☐
I have moderate problems in walking about	☐
I have severe problems in walking about	☐
I am unable to walk about	☐
SELF-CARE	
I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*	
I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐

PAIN / DISCOMFORT	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐
ANXIETY / DEPRESSION	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

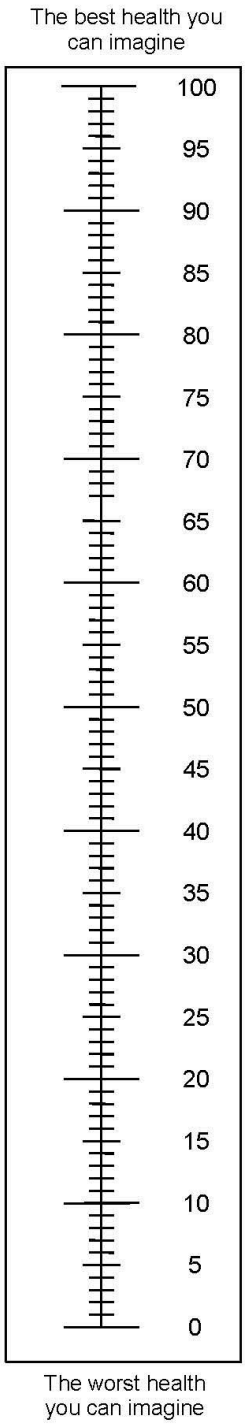
100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



SECTION THREE

SYMPTOMS SURVEY

We would like to ask you some questions that will help us to better understand chronic breathlessness, unintentional weight loss or use of medicines for pain management, whichever is relevant.

Please tick the boxes and provide answers where appropriate to questions that are applicable to you.

If you have experience of using medicines to manage pain, please turn to page 9.

If you have experience of chronic breathlessness please turn to page 11

If you have experience of unintentional weight loss, please turn to page 13.

If you answered No to all the answers above, please go to page 14.

SECTION A

USING MEDICINES TO MANAGE PAIN

Please answer only if you have been prescribed medicines to manage pain in the last twelve months.

If you have not, please go to page 11 Section B

1) Over the last 12 months, how has your pain been?

No pain at all	A little pain	Moderate pain	Severe pain	Overwhelming pain
☐	☐	☐	☐	☐

2) How long have you been affected by pain?

_____

3) What medications are you currently taking to manage your pain?

_____

_____

_____

4) Have you talked to your GP or another health professional about your pain?

Yes	No
☐	☐

5) Please could you tell me a bit more about your answer above? (e.g., who did you talk to? What happened from this discussion? If you answered no, please go to question 6)

_____

_____

6) Do you feel that you had the opportunity to talk about using pain medications with your general practitioner or another health professional?

Yes	No
☐	☐

7) Did you have any initial concerns about taking the pain medications you were prescribed?

Yes	No
☐	☐

8) If yes, what concerns did you have?

_____

_____

_____

9) Have your pain medicines caused you any problems (i.e. side effects)?

Yes	No
☐	☐

10) If so, what problems have they caused?

_____

_____

_____

11) Have your painkillers caused you any problems with the following? *Please tick all that apply*

	Yes	No		Yes	No
Nausea (feeling sick)	☐	☐	Drowsiness/sleepiness	☐	☐
Vomiting (being sick)	☐	☐	Constipation	☐	☐
Memory	☐	☐	Fitting	☐	☐
Confusion	☐	☐	Falls	☐	☐
Attention/concentration	☐	☐	Headaches	☐	☐
Seeing or hearing things that are not	☐	☐	Other	☐	☐

If other, please state: _____

12) Do you take/use pain medicines in the way the health professional suggested? [If answered 'Yes' skip to question 14]

Yes ☐ No ☐

13) If no, please explain more.

_____

_____

_____

_____

14) If you have made changes to taking your pain medications, did you discuss this with your GP or health professional?

Yes ☐ No ☐

15) How often are your pain and pain medications reviewed?

_____

SECTION B

BREATHLESSNESS

Please answer only if you have suffered with breathlessness for most days in the last month

(if you have none, go to page 13 section C)

1) On average over the **past month**, how would you describe his/her breathlessness? (Please tick **one** that best describes your breathlessness).

I am not troubled by breathlessness except on strenuous exercise ☐

I am breathless when hurrying on the level, or walking up a slight hill ☐

I walk slower than most people on the level, or stop after a mile or so, or stop after 15 minutes at my own pace, ☐

I stop for breath after walking about 100 yards or after a few minutes on level ground ☐

I am too breathless to leave the house, or I am breathless undressing ☐

2) How long have you experienced breathlessness?

less than 6 months ☐ between 6 months and 1 year ☐ Over 1 year ☐

3) Does your breathlessness affect your normal day-to-day activities?

Never	Rarely	Sometimes	Often	Very Often	Always
☐	☐	☐	☐	☐	☐

4) Do you feel anxious or depressed **because of your breathlessness**?

Never	Rarely	Sometimes	Often	Very Often	Always
☐	☐	☐	☐	☐	☐

5) Have you had to give up or change any of the following **because of your breathlessness**?

Please specify where appropriate.

☐ Hobbies _____

☐ Exercise _____

☐ Family Roles e.g. looking after family members_____

☐ Social Roles e.g. meeting friends_____

☐ Work/Volunteer Roles _____

☐ Sexual Activity _____

☐ I have not had to give up or change anything

6) Who do you normally talk to **about your breathlessness**?

General practitioner (GP)	☐	Heart Failure nurse	☐
Practice Nurse	☐	Macmillan nurse	☐
Healthcare Assistant	☐	Long term conditions nurse	☐
Respiratory specialist doctor	☐	Family/friends	☐
Respiratory nurse	☐	No-one	☐
Heart Failure specialist doctor	☐	Other (please specify)	_____

7) Roughly, how often do you see a GP, nurse, or other health professional from your GP surgery **about your breathlessness?**

Every week	Every month	Every three months	Every six months	Yearly	Other (please specify)
☐	☐	☐	☐	☐	_____

8) Does your GP, nurse, or other health professional from your GP surgery ask you about how breathlessness **affects your daily life?**

Yes	☐	No	☐	Not sure	☐

9) What treatments **for your breathlessness** have been organized by your GP, nurse, or other health professional from your GP surgery **in addition to your usual treatment (e.g. inhalers or heart tablets)?** (tick all that apply)

Pulmonary Rehabilitation	☐	Psychological Treatments	☐
Breathing Exercise Techniques	☐	Morphine-like medicines	☐
Handheld Fan	☐	Oxygen	☐
Anxiety Treatment	☐	Other (please specify)	_____

10) **Do you have any of the following conditions?**

COPD (also called emphysema or chronic bronchitis)	☐	Other cancer	☐
Heart disease	☐	Asthma	☐
Lung Cancer	☐	Other (please specify)	_____

SECTION C

UNINTENTIONAL WEIGHT LOSS

Please answer if you have lost weight, without trying in the last 12 months

Appetite

1) Has how much you eat changed in the last 12 months?

Yes, I eat more ☐ No, it's the same ☐ Yes, I eat less ☐

2) My appetite is currently:

Very good ☐ Good ☐ Average ☐ Poor ☐ Very poor ☐

3) Currently, how does food taste to you?

Very good ☐ Good ☐ Average ☐ Bad ☐ Very bad ☐

Weight loss:

4) In the last 12 months, roughly how much weight do you think you have lost?

A few pounds ☐ Half a stone ☐ A stone ☐ Over a stone ☐ Not sure ☐

5) Are you worried about your weight loss?

Yes ☐ No ☐ Not sure ☐

6) Have you mentioned your weight loss to anyone?

A hospital Doctor	☐	Your spouse	☐
Your GP	☐	Family member or friend	☐
Practice nurse	☐	Other person	☐
Another nurse	☐	If other people, please specify	
Carer	☐	_____	

7) Did any of the above weigh you?

Yes ☐ No ☐ Can't remember ☐

8) Have any of the following offered you advice on how to gain weight?

A hospital Doctor	☐	Your spouse	☐
Your GP	☐	Family member or friend	☐
Practice nurse	☐	Other person?	☐

Another nurse	☐	Can't remember	☐
Carer	☐	If other person, please specify_____	

9) What advice/help were you given?

A change in your diet	☐	Can't remember	☐
A referral to your dietitian	☐	Other help?	☐
A new medicine prescribed for you	☐	If other help, please specify:_____	

Are you happy for us to contact you for a more detailed follow-up interview on your experience of any of the symptoms above?

Yes ☐ No ☐

Preferred Contact Detail

Telephone_____ **Mobile** _____

Date of Birth _____

Signature _____

Thank you for completing the questionnaire

Appendix 2: PACE study case note review proforma and UWL case note review proforma

PACE

Proactive Anticipatory Care Evaluation

Baseline data collection (Records)

Patient Name: _____

Date: _____

NB. Unless a value is needed, please tick the appropriate box			
Date of data collection	☐☐/☐☐/☐☐☐☐		
Has informed consent been taken?		Yes ☐	No ☐
If yes, state type of consent:			
Written ☐		Witnessed verbal observed ☐	
How was the patient invited to the study			
Intervention		**Control**	
ICC ☐	Care Home ☐	GP ☐	Care Home ☐
Has the patient nominated a carer to take part in the study? (those lacking capacity)		Yes ☐	No ☐
Type of consultee	Personal ☐	Nominated ☐	
PATIENT DEMOGRAPHICS			
Date of birth	☐☐/☐☐/☐☐☐☐		
Gender	Female ☐	Male ☐	
Ethnicity			
White ☐	Mixed/multiple ethnic groups ☐	Asian/Asian British ☐	
Black African/Black Caribbean/Black British ☐	Other ethnic group ☐	Prefer Not to say ☐	Not recorded ☐
Relationship Status			
marital status:			
Single ☐	Married/civil partnership ☐	Separated ☐	Divorced ☐ Widowed ☐ Not recorded ☐
Living situation:			
Spouse/partner ☐	Other family ☐	Alone ☐	Others _____
Postcode	☐☐☐☐ ☐☐☐		

Medical diagnosis	
C0-morbidities	**others**
i. _____ ii. _____ iii. _____ iv. _____ v. _____ vi. _____ vii. _____ viii. _____ ix. _____	

Clinical information	
Weight	☐ **Kg**
Preferred place of care (please specify): _____	

Australia-Modified Karnofsky Performance Status (AKPS)	
Scale (%), 0-100	
AKPS ASSESSMENT CRITERIA	☐ **%**

Activity of daily living (Barthel 10)	
Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items (this can be gotten from patients' record or a relative)	
Bowels score: _____ Bladder *score:*_____ Grooming *score:* _____ Toilet use *score:*_____ Feeding *score:*_____ Transfer *score:*_____ Mobility score:_____ Dressing score:_____ Stairs score:_____ Bathing:_____	*Total Score:* _____

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)				
Over the <u>last 2 weeks</u>, how often have you been bothered by any of the following problems?				
	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Total Score _____	_____+	_____+	_____+	_____+
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?				
Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult	
☐	☐	☐	☐	
<u>Scoring notes.</u> Scores represent: **0-5 = mild 6-10 = moderate 11-15 = moderately severe 16-20 = severe depression**				

GAD-7 Anxiety				
Over the last 2 weeks, how often have you been bothered by the following problems? *(circle to indicate your answer)*				
	Not at all	Several days	More than half the days	Nearly every day
Feeling nervous, anxious or on edge	0	1	2	3
Not being able to stop or control worrying	0	1	2	3
Worrying too much about different things	0	1	2	3
Trouble relaxing	0	1	2	3
Being so restless that it is hard to sit still	0	1	2	3
Becoming easily annoyed or irritable	0	1	2	3
Feeling afraid as if something awful might happen	0	1	2	3
Column totals:	___ +	___ +	___ +	___ +
		= Total Score _____		
If you checked off <u>any</u> problems, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people?				
Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**	
☐	☐	☐	☐	
Scores represent: 0-5 mild 6-10 moderate 11-15 moderately severe anxiety 15-21 severe anxiety				

Intervention delivered Components
Medication Prescribing recommendations

STUDY COMPLETION								
Has the patient completed all study questions?	Yes ☐			No ☐				
Place of primary care achieved	Yes ☐			No ☐				
Details: _____								
If no, please state reason (and complete study withdrawal form if appropriate)								
Study withdrawal (if withdrawn, complete Study Withdrawal Form) ☐	Lost to follow up ☐			Died ☐				
Date of withdrawal	☐☐/☐☐/☐☐☐☐							
If died please state actual place of death								
Hospital ☐	Care home ☐	Home/personal residence ☐	Hospice Setting ☐	Other:				
Date of death	☐☐/☐☐/☐☐☐☐							
Would patient like to receive a summary of study results?	Yes ☐			No ☐				
Name:								
Preferred method of contact:	Telephone ☐	Email ☐	Post ☐	Other please specify _____				
Telephone:								
Email:								
Address:								
Best time to contact you:	Morning ☐	Afternoon ☐	Evening ☐					
Form completed by (name)								
Signature								
Date	☐☐/☐☐/☐☐☐☐							
END								

Date	**Study ID**	DOB	**No. times weighed in past year**	**Weighed by who?**				**Any investigations**								
				GP Nurse appt/ review	*Com. Nurse*	*GP*	*Other*	***No. of Invx***	*Blood tests*	*Scans*	*Referrals*	*Assessments*	*Diagnoses*	*Treatment*	*Appetite loss*	*Notes*
	01/001															
	01/002															

Appendix 3: Measures used in baseline questionnaire and case note review

Clinical Frailty Scale*

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill - Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In severe dementia, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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DALHOUSIE UNIVERSITY
Inspiring Minds

Electronic Frailty Index

electronic Frailty Index (eFI)		
Categories	**score**	**Measures**
Fit	0 - 0.12	-No or few and well-controlled long-term conditions. -Independent in day to day living activities
Mild Frailty	0.13-0.24	-Slowing up in older age May need assistant with -Personal activities/daily living such as finance, shopping transportation
Moderate Frailty	0.25- 0.36	-Need support with outdoor activities. -Mobility problems -Require help with personal care such as washing and dressing
Severe Frailty	> 0.36	-Range of long-term conditions/multiple morbidity - Dependent on people for personal care

Adapted from Clegg et al. (2016) (131)

Adult Comorbidity Evaluation Score

Adult Comorbidity Evaluation-27

Identify the important medical comorbidities and grade severity using the index. Overall Comorbidity Score is defined according to the highest ranked single ailment, except in the case where two or more Grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score should be designated Grade 3.

Cogent comorbid ailment	Grade 3	Grade 2	Grade 1
Cardiovascular System			
Myocardial Infarct	□ MI ≤ 6 months	□ MI > 6 months ago	□ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	□ Unstable angina	□ Chronic exertional angina □ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) □ Recent (≤ 6 months) coronary stent	□ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms □ Angina pectoris not requiring hospitalization □ CABG or PTCA (>6 mos.) □ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	□ Hospitalized for CHF within past 6 months □ Ejection fraction < 20%	□ Hospitalized for CHF >6 months prior □ CHF with dyspnea which limits activities	□ CHF with dyspnea which has responded to treatment □ Exertional dyspnea □ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	□ Ventricular arrhythmia ≤ 6 months	□ Ventricular arrhythmia > 6 months □ Chronic atrial fibrillation or flutter □ Pacemaker	□ Sick Sinus Syndrome □ Supraventricular tachycardia
Hypertension	□ DBP≥130 mm Hg □ Severe malignant papilledema or other eye changes □ Encephalopathy	□ DBP 115-129 mm Hg □ DBP 90-114 mm Hg while taking antihypertensive medications □ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	□ DBP 90-114 mm Hg while not taking antihypertensive medications □ DBP <90 mm Hg while taking antihypertensive medications □ Hypertension, not otherwise specified
Venous Disease	□ Recent PE (≤ 6 mos.) □ Use of venous filter for PE's	□ DVT controlled with Coumadin or heparin □ Old PE > 6 months	□ Old DVT no longer treated with Coumadin or Heparin

Peripheral Arterial Disease	□ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago □ Untreated thoracic or abdominal aneurysm (≥6 cm)	□ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago □ Chronic insufficiency	□ Intermittent claudication □ Untreated thoracic or abdominal aneurysm (< 6 cm) □ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	□ Marked pulmonary insufficiency □ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment □ Chronic supplemental O_2 □ CO_2 retention (pCO_2 > 50 torr) □ Baseline pO_2 < 50 torr □ FEV1 (< 50%)	□ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities □ FEV1 (51%-65%)	□ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment □ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	□ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	□ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	□ Chronic hepatitis or cirrhosis without portal hypertension □ Acute hepatitis without cirrhosis □ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	□ Recent ulcers(≤ 6 months ago) requiring blood transfusion	□ Ulcers requiring surgery or transfusion > 6 months ago	□ Diagnosis of ulcers treated with meds □ Chronic malabsorption syndrome □ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	□ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	□ Uncomplicated acute pancreatitis □ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	□ Chronic pancreatitis w/o complications
Cogent comorbid ailment	**Grade 3**	**Grade 2**	**Grade 1**
Renal System			
End-stage renal disease	□ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis □ Acute dialysis	□ Chronic Renal Insufficiency with creatinine >3 mg% □ Chronic dialysis	□ Chronic Renal Insufficiency with creatinine 2-3 mg%.

Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	□ Hospitalization ≤ 6 months for DKA □ Diabetes causing end-organ failure □ retinopathy □ neuropathy □ nephropathy* □ coronary disease* □ peripheral arterial disease*	□ IDDM without complications □ Poorly controlled AODM with oral agents	□ AODM controlled by oral agents only
Neurological System			
Stroke	□ Acute stroke with significant neurologic deficit	□ Old stroke with neurologic residual	□ Stroke with no residual □ Past or recent TIA
Dementia	□ Severe dementia requiring full support for activities of daily living	□ Moderate dementia (not completely self-sufficient, needs supervising)	□ Mild dementia (can take care of self)
Paralysis	□ Paraplegia or hemiplegia requiring full support for activities of daily living	□ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	□ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	□ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	□ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	□ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	□ Recent suicidal attempt □ Active schizophrenia	□ Depression or bipolar disorder uncontrolled □ Schizophrenia controlled w/ meds	□ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	□ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	□ Connective Tissue Disorder on steroids or immunosuppressant medications	□ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	□ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	□ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	□ Asymptomatic HIV+ patient. □ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	□ Uncontrolled cancer □ Newly diagnosed but not yet treated □ Metastatic solid tumor	□ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	□ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago

Leukemia and Myeloma	□ Relapse □ Disease out of control	□ 1st remission or new dx <1yr □ Chronic suppressive therapy	□ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	□ Relapse	□ 1st remission or new dx <1yr □ Chronic suppressive therapy	□ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	□ Delirium tremens	□ Active alcohol abuse with social, behavioral, or medical complications	□ H/o alcohol abuse but not presently drinking
Illicit Drugs	□ Acute Withdrawal Syndrome	□ Active substance abuse with social, behavioral, or medical complications	□ H/o substance abuse but not presently using
Body Weight			
Obesity		□ Morbid (i.e., BMI ≥ 38)	

Adapted from Piccirillo et al. (189)

Rev November 2003 Clinical Outcomes Research Office
Washington University School of Medicine

Appendix 4: PACE study ethics and governance approvals

NHS ethics approval letter

NHS
Health Research Authority
Yorkshire & The Humber - Bradford Leeds Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Telephone: 0207 1048 088

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

24 January 2019

Professor Fliss Murtagh
Allam Medical Building
University of Hull
Cottingham Road
Hull
HU6 7RX

Dear Professor Murtagh

Study title:	**Proactive Anticipatory Care Evaluation (PACE) study**
REC reference:	**18/YH/0470**
Protocol number:	**N/A**
IRAS project ID:	**250981**

Thank you for your submission of 17 January 2019, 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 Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

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, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non-registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Introduction leaflet]	2	19 September 2018
Copies of advertisement materials for research participants [Introduction leaflet]	3	09 January 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [evidence of sponsorship insurance or indemnity]		18 October 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [evidence of sponsorship insurance or indemnity]		24 September 2018
Interview schedules or topic guides for participants [patient topic guide (breathlessness)]	2	19 September 2018
Interview schedules or topic guides for participants [health professional topic guide (Breathlessness)]	2	19 September 2018
Interview schedules or topic guides for participants [patient topic guide (pain medicine)]	2	19 September 2018
Interview schedules or topic guides for participants [Carers topic guide-pain medicine]	2	19 September 2018
Interview schedules or topic guides for participants [health professionals topic guide (pain medicine)]	2	19 September 2018
Interview schedules or topic guides for participants [patient/care topic guide (unintentional weight loss)]	2	19 September 2018
Interview schedules or topic guides for participants [health professional topic guide (unintentional weight loss)]	2	19 September 2018
IRAS Application Form [IRAS_Form_23112018]		23 November 2018
Letter from funder [confirmation of scholarship]		03 January 2017
Letter from sponsor [letter of sponsorship]		16 October 2018
Letter from sponsor [letter of sponsorship]		16 October 2018
Letters of invitation to participant [Letter of invitation]	3	09 January 2019
Letters of invitation to participant [Letter of invitation with track changes]	3	09 January 2019

Non-validated questionnaire [Baseline questionnaire (those with capacity)]	2	19 September 2018
Non-validated questionnaire [baseline questionnaires (without capacity)]	2	19 September 2018
Non-validated questionnaire [Baseline questionnaire (control group)]	2	19 September 2018
Non-validated questionnaire [Follow up questionnaire (with capacity)]	2	19 September 2018
Non-validated questionnaire [follow up questionnaire (without capacity)]	2	19 September 2018
Non-validated questionnaire [Questionnaire for patients information (records)]	3	09 January 2019
Non-validated questionnaire [Questionnaires for patient information (records) with track changes]	3	09 January 2019
Other [Response to REC amendment]		14 January 2019
Other [University of Hull lone worker policy]		15 December 2016
Participant consent form [Patient consent form]	3	08 January 2019
Participant consent form [patient informed consent form (interview)]	3	08 January 2019
Participant consent form [informed consent form (interview) with track changes]	3	08 January 2019
Participant consent form [Informed consent form with track changes]	3	08 January 2019
Participant consent form [consultee declaration form]	3	08 January 2019
Participant consent form [consultee declaration form with track changes]	3	08 January 2019
Participant information sheet (PIS) [participants information sheet (cases)]	3	08 January 2019
Participant information sheet (PIS) [participant information sheet (cases) with track changes]	3	08 January 2019
Participant information sheet (PIS) [participants information sheet (control group)]	3	08 January 2019
Participant information sheet (PIS) [participant information sheet (control group) with track changes]	3	08 January 2019
Participant information sheet (PIS) [patient/family information sheet (interviews)]	3	08 January 2019
Participant information sheet (PIS) [Patient/carer information sheet with (interview) with track changes]	3	08 January 2019
Participant information sheet (PIS) [Health professional information sheets (interviews)]	3	08 January 2019
Participant information sheet (PIS) [health professionals information sheet (interview) with track changes]	3	08 January 2019
Participant information sheet (PIS) [Consultee Information sheet]	1	08 January 2019
Research protocol or project proposal [Project protocol]	10	09 January 2019
Summary CV for Chief Investigator (CI) [Fliss CV]	1	18 September 2018
Summary CV for student [Helene CV]	1	19 September 2018
Summary CV for student [Gochi CV]	1	19 September 2018
Summary CV for student [Sophie's CV]	1	19 September 2018
Summary CV for supervisor (student research) [Fliss CV]	1	19 September 2018
Summary CV for supervisor (student research) [Jason CV]	1	19 September 2018
Summary CV for supervisor (student research) [Joseph CV]	1	19 September 2018
Summary CV for supervisor (student research) [Miriam's CV]	2	19 September 2018
Summary, synopsis or diagram (flowchart) of protocol in non-technical language [Summary of project]	2	17 August 2018

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

18/YH/0470	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely
pp

Sarah Prothero

Dr Janet Holt
Chair

Email: nrescommittee.yorkandhumber-bradfordleeds@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Andrew Taylor, University of Hull*

Dr Marie Girdham, NHS East Riding of Yorkshire Clinical Commissioning Group

HRA approval letter

Professor Fliss Murtagh
Allam Medical Building
University of Hull
Cottingham Road
Hull
HU6 7RX
fliss.murtagh@hyms.ac.uk

Email: hra.approval@nhs.net

22 March 2019 **[Re-issued 04 April 2019]**

Dear Professor Murtagh

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Proactive Anticipatory Care Evaluation (PACE) study**
IRAS project ID:	**250981**
REC reference:	**18/YH/0470**
Sponsor	**University of Hull**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations in England and Wales should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter. You should then work with each organisation that has confirmed capacity and capability and provide clear instructions when research activities can commence.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Professor Fliss Murtagh
Tel: 01482 463 164
Email: fliss.murtagh@hyms.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

IRAS project ID	250981

Your IRAS project ID is **250981**. Please quote this on all correspondence.

Yours sincerely

Gemma Oakes
Assessor

Email: hra.approval@nhs.net

Copy to: *Dr Andrew Taylor, University of Hull [Sponsor Contact]*
a.f.taylor@hull.ac.uk
Dr Marie Girdham, NHS East Riding of Yorkshire Clinical Commissioning Group [Lead NHS R&D Contact]
Marie.girdham@nhs.net

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

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Copies of advertisement materials for research participants [Introduction leaflet]	2	19 September 2018
Copies of advertisement materials for research participants [Introduction leaflet]	3	09 January 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Certificate]		24 September 2018
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HRA Schedule of Events [Site Type 1 - ICC]	1	20 March 2019
HRA Schedule of Events [Site Type 2 - Care]	1	20 March 2019
HRA Schedule of Events [Site Type 3 - GP Practices]	1	04 April 2019
HRA Statement of Activities [Site Type 1 - ICC]	1	18 January 2019
HRA Statement of Activities [Site Type 2 - Care Homes]	1	18 January 2019
HRA Statement of Activities [Site Type 3 - GP Practices]	1	18 January 2019
Interview schedules or topic guides for participants [patient topic guide (breathlessness)]	2	19 September 2018
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capacity)]		
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Participant information sheet (PIS) [Control Participant Information Sheet]	3	08 January 2019
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Summary CV for supervisor (student research) [Miriam's CV]	2	19 September 2018
Summary, synopsis or diagram (flowchart) of protocol in non-technical language [Summary of project]	2	17 August 2018

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	The applicant has confirmed The Jean Bishop Integrated Care Centre will act as a Research Site in the study. Submission of an amendment is required to include further Research Sites in the study.
2.1	Participant information/consent documents and consent process	Yes	Following REC review, very minor non-substantial changes were made to the participant information sheets to comply with HRA Standards. REC review was not required.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	There are 3 site types participating in the study. A statement of activities has been submitted for all 3 site types and the sponsor is not requesting and does not expect any other site agreement to be used.
4.2	Insurance/indemnity arrangements assessed	Yes	The sponsor has confirmed the design, management and conduct of the study will be covered under its insurance arrangements. A Certificate of Insurance has been provided.
4.3	Financial arrangements assessed	Yes	External funding has been secured from University of Hull. No funding will be provided to Site Types 1 and 2. Funding will be provided to Site Type 3, a detailed in Schedule 1 of the

Section	Assessment Criteria	Compliant with Standards	Comments
			Statement of Activities.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	Following REC review, very minor non-substantial changes were made to the participant information sheets to comply with GDPR. REC review was not required.
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	Following REC review, very minor non-substantial changes were made to the participant information sheets to comply with HRA Standards. REC review was not required.
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

There are 3 site types participating in the study. Research activities at the participating NHS sites is as follows:

- **Site Type 1 – Jean Bishop Integrated Care Centre – ICC (Intervention Group):**

  Patient Participants: these organisations will screen, identify and approach potential patient participants for the study. A member of the External Research Team will undertake the consent process and remaining research activities.

Health Care Professionals: A member of the External Research Team will recruit eligible staff participants, undertake the consent process and remaining research activities.

- **Site Type 2 – Care Homes (Intervention Group):**

  Patient Participants: these organisations will screen, identify and approach potential patient participants for the study. A member of the External Research Team will undertake the consent process and remaining research activities.

  Health Care Professionals: A member of the External Research Team will recruit eligible staff participants, undertake the consent process and remaining research activities.

- **Site Type 3 – GP Practices (Control Group):** these organisations will carry out search of patient records to identify potential patient participants, and send mail out to them. External research staff will access/review medical records.

  All remaining research activities will take place off-site.

Please note that the remit of HRA Approval is limited to the NHS involvement in the study. Research activity undertaken at non-NHS sites is therefore not covered and the research team should make appropriate alternative arrangements with relevant management at these organisations to conduct the research there.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).

The sponsor position and training requirements for the 3 types of participating NHS sites are appropriate for the study, as follows:

- **Site Type 1 - Jean Bishop Integrated Care Centre – ICC (Intervention Group):** A Local Principal Investigator is required and has been identified.

- **Site Type 2 – Care Homes (Intervention Group):** A Local Principal Investigator is required and has been identified.

- **Site Type 3 – GP Practices (Control Group):** A Local Collaborator is required at the participating NHS sites.

GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

In respect of HR Guidelines, the following arrangements are expected:

- **Site Type 1 - Jean Bishop Integrated Care Centre – ICC (Intervention Group):** Where arrangements are not already in place, network staff (or similar) undertaking any research activities that may impact on the quality of care of the participant, would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

- **Site Type 2 – Care Homes (Intervention Group):** Where arrangements are not already in place, network staff (or similar) undertaking any research activities that may impact on the quality of care of the participant, would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

- **Site Type 3 – GP Practices (Control Group):** As this study is taking place in GP practices you are advised to contact the primary care management function to follow local processes.

Use of identifiable information held by an NHS organisation to identify potential participants should be undertaken by a member of the direct care team for those participants. No additional arrangements (honorary research contracts or letters of access) should be necessary for identification and referral of potential participants at the PICs.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.

- The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.
- Please note the final list of documentation does not match with the final list of REC approved documentation. This is due to the submission of a non-substantial amendment (that does not require submission to REC) in order to bring the study in line with HRA Standards.

CHCP letter of access

Business Support Centre
5, Beacon Way
Hull
HU3 4AE

Telephone: 01482 976948
E-mail: sue.pender@nhs.net

18th April 2019

Letter of Access for Research

Study title: **Proactive Anticipatory Care Evaluation (PACE) Study**

IRAS project ID: **250981**

REC reference: **18/YH/0470**

Dear Ugochinyere Nwulu,

Thank you for submitting your research documents for the above study, for review by City Health Care Partnership's (CHCP CIC) Research Approval Group (RAG).
This letter confirms that the CHCP Research Approval Group (RAG) have reviewed the research documents and has granted you a right of access to conduct research within the organisation for the purpose and on the terms and conditions set out below. This right of access commences today and ends on 17th April 2020 unless terminated earlier in accordance with the clauses below.

The research approval group note the study sponsor as Hull University and thus you do not require an honorary research contract with CHCP. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor in any CHCP care delivery site. You are not entitled to any form of payment or access to other benefits provided by CHCP to employees and this letter does not give rise to any other relationship between you and CHCP, in particular that of an employee.

While undertaking research within CHCP, you will remain accountable to your employer – Hull York Medical School and you are required to follow the reasonable

instructions of Tracy Woodrow, Operational Manager, Jean Bishop Integrated care Centre or those given on her behalf in relation to the terms of this right of access.

The CHCP local research contact is Dr Dan Harman Medical Consultant. We understand that you have made contact with both Tracy and Dan as part of the PACE study pre-set up arrangements (both cc'd into this letter for their assurance that the necessary research governance checks have been completed)

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by CHCP in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You are required to co-operate with CHCP in discharging its duties under the Health and Safety at Work Act 1974 and other health and safety legislation. You must take reasonable care for the health and safety of yourself and others while on premises of CHCP. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, you must notify your employer and CHCP Research Approval Group prior to access.

This letter does not permit you access to confidential patient information without participant consent. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and UK data protection legislation; namely the General Data Protection Regulation (GDPR) 2018 and UK Data Protection Act (DPA) 2018. CHCP will not indemnify you against any liability incurred as a result of any breach of this data protection legislation. It may result in legal action against you and/or your substantive employer. Your substantive employer is responsible for your conduct during this research project and, may in the circumstances described above, instigate disciplinary action against you.

We may terminate your right to access at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably

consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of CHCP or if you are convicted of any criminal offence.

You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Please note that CHCP accepts no responsibility for damage to or loss of personal property. Please ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged.

Yours sincerely

Sue Pender

Lead Practitioner Quality improvement

On behalf of CHCP's Research Approval Group

Hull CCG letter of access

NHS
East Riding of Yorkshire
Clinical Commissioning Group

14/04/2019

Research and Development Service
(Supporting the four Humber CCGs, Hull, East Riding, North and North East Lincolnshire)
Health Place
Wrawby Road
Brigg
North Lincolnshire
DN20 8GS

Telephone: (01652) 251088
Fax: (01652) 258110
E-mail: angie.beacroft@nhs.net
Website: www.eastridingofyorkshireccg.nhs.uk

Ugochinyere Nwulu
HYMS
University of Hull
Cottingham Road
HU6 7RX

Dear Ugochinyere

Letter of Access for Research

Title of Study: Proactive Anticipatory Care Evaluation (PACE) study

Reference No: 250981

CCG Areas: Hull CCG

This letter confirms that the R&D Service have reviewed the Research Passport and has granted you a right of access to conduct research through the independent contractors based within the above CCG(s) for the purpose and on the terms and conditions set out below. This right of access commences on **15/04/2019** and ends on **31/12/2019** unless terminated earlier in accordance with the clauses below.

The information supplied about your role has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that pre-engagement checks have been carried out.

You have a right of access to conduct research based on requirements outlined in the letter of assurance from the Health Research Authority (HRA) and schedule of events. You must also act in accordance with the principles of the UK policy framework for Health and Social Care Research (2017).

You are considered to be a legal visitor to premises of the independent contractors based within the above CCG(s). This letter does not give you entitlement to any form of relationship with, payment or access to other benefits provided by them. While undertaking research you

will remain accountable to your employer Hull York Medical School and you are required to follow the reasonable instructions of Dr Marie Girdham,Research and Development Lead of the R&D Service or those given on her behalf.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by the R&D Service in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You are required to co-operate with the independent contractor(s) based within the above CCG(s) in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation. You must take reasonable care for the health and safety of yourself and others while on premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If your current role or involvement in research changes, any of the information provided in your Research Passport changes, you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, you must notify your employer and the R&D Service prior to commencing your research role.

This letter does not permit you access to confidential patient information without consent. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and UK data protection legislation; namely the General Data Protection Regulation (GDPR) 2018 and UK Data Protection Act (DPA) 2018. The independent contractors based within the above CCG(s) will not indemnify you against any liability incurred as a result of any breach of this data protection legislation. It may result in legal action against you and/or your substantive employer. Your substantive employer is responsible for your conduct during this research project and, may in the circumstances described above, instigate disciplinary action against you.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to

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amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence.

You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you must stop undertaking any regulated activity immediately.

Yours sincerely

Dr Marie Girdham
Research & Development Lead Manager (Humber)
Research and Development Service

Appendix 5: PACE study information sheets

PACE
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Care Evaluation

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Clinical Commissioning Group

Patient Information Sheet

A large-print version of this sheet is available on request.

Invitation to take part in a research study

We would like you to take part in a research study. To help you to decide if you would like to take part, we have written this information sheet. It should explain why the research is being done, what you will be asked to do, and why we would like you to take part. Please take your time to read the information. You can talk with your friends or family about it if you like.

What is this study about?

We are trying to find out how the new service you have been invited to or just visited has helped improve your overall health and wellbeing; compared to how you have been cared for until now. Your answers will help in the improvement of this service.

Why have I been invited to take part?

We would like you to take part in this study because you have recently been invited to attend an appointment at the new service at the Jean Bishop integrated care centre or at you care home by your GP. Your GP has identified you as being eligible for this study.

What will happen if I take part?

If you take part in the study, you will be asked to sign a consent form. You will be asked to complete a short questionnaire at the first meeting either at the Jean Bean Integrated Centre or at the care home you live in. Someone from the research team will help you fill in the questionnaire. If you are unable to complete the questionnaire at the first meeting, another date and time convenient for you will be set. It will take you about 45minutes to complete the questionnaire. Someone from the research team will contact you to ask if you are happy to complete a shorter version of the questionnaire in 2-4 weeks and in 10-14weeks time.

We would like you to answer the questions as honestly as you can and there are no right or wrong answers. You will be asked if you would like to nominate a family member or carer to help fill in the questionnaire for you. There is a separate consent form (consultee form) to be completed by the nominated person, please ask for a copy of this.

What else will happen if I take part?

Some people taking part will be asked if they would like to take part in an interview with a researcher if they are affected by any of the following; chronic breathlessness, unintentional weight loss or use of medicine for pain and possible side effects. The interview can be held on the same day you complete the questionnaire or at a different time and place if it is easier for you.

If you take part, a member of the research team will do the interview and it will last around 45 minutes. Each topic will have a slightly different focus but will involve questions around your experience of one of topics listed above. It will also involve your opinion on caring experience, management of care, communication with health professionals, information and support needs, and the impact or potential concerns around these issues.

Do I have to take part?

No. It is up to you to decide if you would like to take part. If you decide not to take part, this will be noted and you will not be asked again. You will also continue to receive care and support from your GP practice or any health professional as usual. If you were to take part, you can still change your mind and stop taking part at any time without giving any reason.

What are the possible benefits of taking part in the study?

It is unlikely that there will be any direct personal benefit for you taking part. However, the information that you will give us will help decide if your overall health and wellbeing has improved by using this new service and give us ways to improve this service in the future.

Are there potential risks of taking part?

There is no significant risk in taking part, other than the time the study will take. However if you have any worries, you can talk about them with the research team or your GP. We would like to stress that taking part is up to you and you can stop taking part at any time without reason.

Will my involvement be confidential?

Yes. All the information we collect will be kept confidential, to fit with the General Data Protection Regulation (GDPR) 2018. The University of Hull is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Hull will keep identifiable information about you for 10 years after the study has finished.

Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information at https://www.hyms.ac.uk/research/research-centres-and-groups/wolfson/pace or by contacting PACE@hyms.ac.uk.

The GP Practice will collect information from you and your medical records for this research study in accordance with our instructions.

The GP practice will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Hull and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Your GP Practice will pass these details to University of Hull along with the information collected from you and your medical records. The only people in the University of Hull who will have access to information that identifies you will be people who need to contact you to collect data/information or audit the data collection process. The people who analyse the

information will not be able to identify you and will not be able to find out your name, NHS number or contact details.
The research team from the University of Hull will keep identifiable information about you from this study for 10 years after the study has finished.

Expenses

You will be provided with prepaid envelopes, if needed, to return any documents to the research team. There will be no other costs to you.

What will happen to the results of the research study?

The results from this study will be written as a report for the NHS Hull clinical commissioning group (NHS Hull CCG). The results will be written up into journals, presented at conferences and public engagement events. If you would like to receive a summary of the study result, please inform someone from the research team. All personal details will be anonymised in all publications and public documents.

If I find it necessary to make a complaint, who should I contact?

If you have any concerns, questions or complaints about this research, you can contact Dr Maureen Twiddy (01482 463279, 8am to 5pm weekdays) or email Maureen.Twiddy@hyms.ac.uk Dr Twiddy is based at University of Hull but is independent of the research team.

How can I get involved in the study?

Thanks you for taking the time to read this information sheet. **If you would like to know more, please contact the research team using the details below:**

Dr Mabel Okoeki (Project Lead)

Telephone: (01482) 463728

Email: PACE@hyms.ac.uk

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PATIENT AND FAMILY CARER INFORMATION SHEET

Qualitative Interviews

A large-print version of this sheet is available on request.

Introduction

We would like to invite you to take part in our study. Your participation will help us to understand your thoughts on and experiences of one of the following topics:

- Chronic breathlessness
- Unintentional weight loss
- Use of medicines for pain

To help you to decide if you would like to take part, we have created this information sheet. It explains why the research is being done, what you will be asked to do, and why we are asking you to take part. Please take time to read the following information carefully and talk about it with others if you wish. You can contact someone from the research team and ask them to explain anything that is not clear to you. The Wolfson Palliative Care Research Centre based at the University of Hull runs the study.

What is the study about?

The purpose of this study is to explore your experiences of chronic breathlessness, unintentional weight loss, and the use of medicines for pain and possible side effects. This will help us better understand these problems as well as how they can be managed better.

Why have I been invited to take part?

You have been invited to take part in an interview because you have indicated that you have experience of or care for someone who is affected by chronic breathlessness, unintentional weight loss, or use medicines for pain. You have indicated when you completed the survey questionnaires that you are willing to be contacted about taking part in an interview or have a family member who might also want to participate but was not present on your assessment visit.

Do I have to take part?

No. It is up to you to decide if you would like to take part. If you decide not to take part, this will be noted and you will not be asked again. You will also continue to receive care and support from your GP practice or any health professional as usual. If you to take part, you can change your mind and stop taking part at any time without giving any reason.

What will happen if I take part?

If you take part, you will be asked to sign a consent form and then take part in an interview with one of our researchers, which will take about 45 minutes. The interview can be at the Jean Bishop Integrated Care Centre, your resident care home or at a place and time convenient for you. Each topic will have a slightly different focus but will involve questions around your experience of one of topics listed above. The interview sessions will be audio-recorded to aid transcription. After the interview, members of the research team will carry out the transcription. Information collected, which can identify you will be anonymised at the time of the transcription.

What are the possible benefits of taking part in the study?

Although there is no direct benefit, you may value the chance to talk through your experiences. However, the information that you give us will help us to better understand experiences of chronic breathlessness, unintentional weight loss and effects of use of pain medicines, so this will help others with these problems in the future.

Are there any potential risks of taking part?

There are no significant risks in taking part. . We would like to stress that taking part is up to you and you can stop taking part at any time without reason and without your medical care or legal rights being affected.

Will my involvement be confidential?

Yes. All the information we collect will be kept confidential, to fit with the General Data Protection Regulation (GDPR) 2018. The University of Hull is the sponsor for this study based in the United Kingdom. We will be using information either from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Hull will keep identifiable information about you for 10 years after the study has finished.

Your rights to access change or move your or his/her information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your or his/her information at https://www.hyms.ac.uk/research/research-centres-and-groups/wolfson/pace or by contacting PACE@hyms.ac.uk.

The research team from the University of Hull will collect information from you for this research study in accordance with our instructions.

The research team from the University of Hull will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for you, and to oversee the quality of the study. Individuals from the University of Hull and regulatory organisations may look at your research records to check the accuracy of the research study. Your details will be passed to University of Hull along with the information collected from you. The only people in the University of Hull who will have access to information that identifies you will be people who need to contact you to collect data/information or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

The research team from the University of Hull will keep identifiable information about you from this study for 10 years after the study has finished.

However, if you raise an issue of concern for your health, we may ask your permission to contact your GP or other health professional to seek specific help or advice for you.

Expenses

There will be no other costs to you.

What will happen to the results of the research study?

The results of this study will form a part of three PhD theses. They will be presented at conferences and public engagement events and be written up for publication in academic journals. If you would like to receive a summary of the study findings, please inform the researcher. With your permission, publications may include anonymised quotations.

If I find it necessary to make a complaint, who should I contact?

If you have any concerns, questions or complaints about this research, you can contact Dr Maureen Twiddy (01482 463279, 8am to 5pm weekdays) or email Maureen.Twiddy@hyms.ac.uk Dr Twiddy is based at University of Hull but is independent of the research team.

How can I get involved in the study?

Thank you for taking the time to read this information sheet. **If you would like to know more or wish to take part, please contact the research team using the details below:**

Helene Elliott-Button, Ugochinyere Nwulu or Sophie Pask
Telephone: (01482) 463728
Email: PACE@hyms.ac.uk

Appendix 6: PACE study participant consent forms - baseline questionnaire and qualitative interviews

PACE
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Participant consent form

	Please Initial each box
I confirm that I have read and understood the participant information sheet for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	☐
I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical and legal rights being affected.	☐
I understand that responsible individuals may look at relevant sections of any data collected during this study from the research team, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this data.	☐
I understand that by filling in and signing this form I give permission for my GP records and hospital records to be accessed by the research team for the purpose of this study.	☐
I understand that my information may be subject to review by responsible individuals from the University for monitoring and audit purposes.	☐
I understand that the information collected about me may be published or will be used to support other research in the future, and may be shared anonymously with other researchers.	☐
I agree to take part in the above study	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

Name of witness of oral consent	Date	Signature

☐ Tick here if participant has given consent but is physically unable to sign and has requested a witness

I witness that _____ has agreed to participate in this research study. I confirm that I have initialled the consent statements as per their wishes.

Name of witness (Print)	Date	Signature
Name of person taking consent (Print)	Date	Signature

Office Use Only

Tick the appropriate box once completed

Participant's copy	☐
Research team/site file copy	☐
Medical record's copy	☐

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Care Evaluation

Hull
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Consent Form for Research Participants
(Qualitative Interviews)

	Please Initial each box
I confirm that I have read and understood the participant information sheet for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	☐
I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical and legal rights being affected. Furthermore, I understand that I am able to withdraw my data up to the time of transcription and analysis	☐
I consent to be interviewed and agree to the interview being recorded and direct quotes used during data/result presentation anonymously.	☐
I understand that responsible individuals may look at relevant sections of any data collected during this study from the research team, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this data.	☐
I understand that my information may be subject to review by responsible individuals from the University for monitoring and audit purposes.	☐
I understand that the information collected about me may be published or will be used to support other research in the future, and may be shared anonymously with other researchers.	☐
I agree to take part in the above study.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

Name of witness of oral consent	Date	Signature

☐ Tick here if participant has given consent but is physically unable to sign and has requested a witness

I witness that _____ has agreed to participate in this research study. I confirm that I have initialled the consent statements as per their wishes.

Name of witness (Print)	Date	Signature

Name of person taking consent (Print)	Date	Signature

Office Use Only

Tick the appropriate box once completed

Participant's copy	☐
Research team/site file copy	☐
Medical record's copy	☐

Appendix 7: PACE study interview topic guide

PACE
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Care Evaluation

Clinical Commissioning Group

Unintentional weight loss – Qualitative interviews – patients and caregivers

Interviewer to:

- Note time/date and location of interview
- Welcome and thank participant for agreeing to taking part
- Briefly run through the study aims and information sheet
- Remind that there are no right or wrong answers as each individual's experiences are important
- Confidentiality and audio-recording: only the research team will hear the recording and personal details will be removed. Any quotes used will be anonymous.
- Plan to keep to 30 to 45 minutes but participant can ask for a break when needed
- Any further questions?

- ***Review participant information sheet & sign consent form***
- ***Let the participant know that the recorder has been switched on now***

Question (for interviewee/ interviewees)
1. Could you tell me a little about your health and how it affects you (you both)? a. **Home and family lives** b. **Social lives and activities**
2. As you know, this conversation will mainly be about weight loss. Could you tell me about your weight loss? a. **Any loss in appetite?** ***Prompts –*** ***Timescales – when started, duration*** ***Severity or degree*** ***What they noticed first (clothes, other peoples' comments)*** ***Dietary changes*** ***Loss of appetite*** ***Other symptoms***

3. How does this affect you? ***Prompts –*** ***Symptoms*** ***Weakness*** ***interferes with daily activities – meals, cooking, shopping, housekeeping***
4. What have you tried, if anything, to gain weight? ***Prompt -*** ***Carer's opinion*** ***Dietary changes*** ***Asked your hospital or practice doctor***
5. Where have you looked for help or advice? a. **What do you think of the help and advice that you have received?**
6. What would you like to see being done for someone in your position? ***Prompts –*** ***What information do you think is needed?*** ***What would cause you not to worry as much?***
7. Is there anything else that you would like to tell me? ***Finish off and thank the participant for their time.***

Appendix 8: Systematic review search strategy

EMBASE

1. (Cachexia or starvation or malnutrition or "wasting syndrome" or "muscle strength" or anorexia).sh.
2. (Cachexia* or cachectic* or (weight adj3 loss) or "wasting syndrome" or "muscle loss" or "muscle wasting" or anorexia).mp.
3. 1 or 2
4. (Nutrition* or malnutrition*).mp. and (mass screening or nutrition assessment).sh.
5. ((malnutrition* or nutrition*) adj3 (screen* or assess*)).mp.
6. (tool* or screen* or diagnos* or scale* or identif* or assess* or criteria or measure* or survey* or history* or questionnaire*or quest*).ab.
7. 4 or 5
8. 6 and 7
9. (Child or adolescent or infant).sh.
10. ((child or children or pediatric* or paediatric*) not adult).mp.
11. (animals not (humans and animals)).mp.
12. 9 and 10
13. 11 or 12
14. (3 and 8) not 13
15. limit 14 to (human and yr="2008 -2019" and (adult <18 to 64 years> or aged <65+ years>))

MEDLINE (Ovid)

1. (Cachexia or starvation or malnutrition or "wasting syndrome" or "muscle strength" or anorexia).sh.
2. (Cachexia* or cachectic* or (weight adj3 loss) or "wasting syndrome" or "muscle loss" or "muscle wasting" or anorexia).mp.
3. 1 or 2
4. (Nutrition* or malnutrition*).mp. and (mass screening or nutrition assessment).sh.
5. ((malnutrition* or nutrition*) adj3 (screen* or assess*)).mp.
6. (tool* or screen* or diagnos* or scale* or identif* or assess* or criteria or measure* or survey* or history* or questionnaire*or quest*).ab.
7. 4 or 5
8. 6 and 7
9. (Child or adolescent or infant).sh.
10. ((child or children or pediatric* or paediatric*) not adult).mp.
11. (animals not (humans and animals)).mp.

12. 9 and 10
13. 11 or 12
14. (3 and 8) not 13
15. limit 14 to (human and yr="2008 -Current" and (adult <18 to 64 years> or aged <65+ years>))
16. limit 15 to (male and female and humans and yr="2008 -Current" and ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") and humans)

PsychINFO

1. (Cachexia or starvation or malnutrition or "wasting syndrome" or "muscle strength" or anorexia).sh.
2. (Cachexia* or cachectic* or (weight adj3 loss) or "wasting syndrome" or "muscle loss" or "muscle wasting" or anorexia).mp.
3. "Anorexia Nervosa".mp
4. 1 or 2 not 3
5. (Nutrition* or malnutrition*).mp OR (mass screening or nutrition assessment).mp
6. (tool* or screen* or diagnos* or scale* or identif* or assess* or criter* or measure* or survey* or history* or questionnaire*).mp.
7. ((malnutrition* or nutrition*)adj3(screen* or assess*)).mp
8. (5 and 6) or 7
9. 4 and 8

CINAHL (EBSCO)

1. TX (cachexia or "cancer cachexia" or "wasting syndrome")
2. AB (anorexia or "muscle loss" or "muscle weakness")
3. TI (anorexia or "muscle loss" or "muscle weakness")
4. MJ (cachexia or "cancer cachexia" or "wasting syndrome")
5. 1 or 2 or 3 or 4
6. NOT AB "anorexia nervosa" or NOT MJ "anorexia nervosa"
7. 5 and 6
8. AB (tool* or screen* or diagnos* or scale* or identif* or assess* or criter* or measure* or survey* or history* or questionnaire*)
9. 7 and 8

Appendix 9: Systematic review quality assessment scale

Systematic review - Quality Assessment Scale used for quantitative studies

			Score
1	**Aims/Outcomes**	Defined at outset	*2*
		Implied in paper	*1*
		Unclear	*0*
2	**Sample formation**	Random or total population	*2*
		Quasi random; sequential series in a given setting	*1*
		Selected, historical, other, insufficient information	*0*
3	**Inclusion/Exclusion**	Criteria explicitly described in paper	*2*
		Implied by patient characteristics, setting	*1*
		Unclear	*0*
4	**Subjects described**	Full info	*2*
		Partial info	*1*
		No info	*0*
5	**Power of study calculated**	Yes	*2*
		No	*0*
6	**Outcome measures**	Objective assessment/records	*2*
		Patient-reported/proxy	*1*
		Not explicit	*0*
7	**Cross sectional**	>90% patients enrolled/ approached /available	*2*
		60-90% of subjects	*1*
		< 60% of subjects / no info	*0*
	OR		
	Cohort/Interventional (pre/post)	60% followed up in pre/post or subsequent time points	*2*
		40-60% subjects	*1*
		<40% subjects/no info	*0*
8	**Analysis**	Intention to treat/including all available data	*2*
		Excluding dropouts with evidence of bias corrected or no bias evident	*1*
		Excluding dropouts with not attention to bias or imputing results	*0*
9 - 11	**FOR INTERVENTIONAL TRIALS ONLY**		
9	**Baseline differences between groups**	None or adjusted	*2*
		Differences unadjusted	*1*
		No information	*0*
10	**Unit of allocation (individual/cluster)**	Appropriate	*2*
		Nearly	*1*
		Inappropriate or no control group	*0*
11	**Randomisation / Allocation**	Random	*2*
		Method not explicit	*1*
		Before exclusion of dropouts/not randomised	*0*
	TOTAL	Denominator of 16 for an observational study and 22 for an experimental study	
		Quality score: % score	

Adapted from: Edwards, Adrian, et al. "Judging the 'weight of evidence 'in systematic reviews: introducing rigour into the qualitative overview stage by assessing Signal and Noise." *Journal of Evaluation in Clinical Practice* 6.2 (2000): 177-184.

And: Higginson, Irene J., et al. "Do hospital-based palliative teams improve care for patients or families at the end of life?" *Journal of pain and symptom management* 23.2 (2002): 96-106.

Appendix 10: Systematic Review Results Table 1

Table 1: Characteristics of included studies

	Lead author (year)	Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
1	Agustsson 2012 (1)	Cross-sectional	Hospital OP	Sweden	40	56	Cancer	32.5	●	●		●	●	
2	Aktas 2022 (2)	Cross-sectional	Hospital	Ireland	200	69	Cancer - solid tumours	52	●		●	●	●	
3	Alvarez Del Castillo 2020 (3)	Cross-sectional	Hospital	Mexico	313	88	Cancer - GI	79	●			●	●	
4	Álvaro Sanz 2019 (4)	Controlled	Hospital OP	Spain	295	81	Cancer - Solid tumours	40	●	●			●	
5	Alvaro Sanz 2020 (5)	Cross-sectional	Hospital	Spain	177	77	Cancer - solid tumours	--	●		●	●		QoL
6	Andrew 2009 (6)	Controlled	Hospital	UK	40	56	Cancer - various	IC	*History*			●		Symptoms
7	Araújo 2011 (7)	Cohort	Hospital	Portugal	94	63	CHF	32.4	●	●			●	
8	Aredes 2018 (8)	Cohort	Hospital OP	Brazil	49	50	Cancer - Cervical	IC	●	●	●			QoL
9	Bachmann 2009 (9)	Cross-sectional	Hospital	Germany	198	69	Cancer - Pancreas	39.9	●	●				
10	Bahadir 2019 (10)	Cross-sectional	Hospital OP	Turkey	187	25	COPD	40	●	●		●	●	

Lead author (year)		Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
11	Barajas Galindo 2017 (11)	Cross-sectional	Hospital	Spain	128	69	Cancer	--						
12	Berk 2008 (12)	RCT	Hospital	USA	427	56	Cancer - Metastatic	IC	●	●				
13	Borghi 2019 (13)	Cohort	Hospital	Italy	190	69	Cancer	51	●			●	●	
14	Bozzetti 2009 (14)	Cross-sectional	Hospital	Italy	1307	69	Cancer	39.9	●			●		Symptoms
15	Bullock 2022 (15)	Cross-sectional	Hospital IP	UK	30	69	Cancer	57	●		●	●		
16	Buskermolen 2012 (16)	Cohort	Hospital	Netherlands	20	63	Cancer	50	●	●	●		●	
17	Bye 2013 (17)	Cohort	Hospital	Norway	39	56	Cancer - Pancreas	46	●				●	Symptoms
18	Camus 2014 (18)	Cohort	Hospital care	France	80	77	Cancer - Lymphoma	--						
19	Castillo-Martinez 2012 (19)	Cohort	Hospital	USA	519	86	CHF	39.2	●	●	●		●	
20	Castro 2019 (20)	Cross-sectional	Hospital	Brazil	120	56	Cancer - H&N	35	●	●	●		●	
21	Cavalcante Martins 2019 (21)	Cohort	Hospital IP	Brazil	97	69	Cancer - H&N and GI	37.8	●	●		●		QoL
22	Cavka 2022 (22)	Cohort	Hospital	Slovenia	141	69	Cancer - Prostate	11.4	●	●	●	●		QoL
23	Chen 2020 (23)	Cross-sectional	Hospital	China	1001	50	Cancer - GI	36.3	●	●		●		

	Lead author (year)	Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
24	da Rocha 2019 (24)	Cohort	Hospital OP	Brazil	60	56	Cancer - GI	55	●	●	●	●		
25	de Clercq 2021 (25)	RCT	Hospital	Netherlands	24	44	Cancer - GI	IC	●		●			
26	Debieuvre 2017 (26)	Cross-sectional	Hospital	France	539	69	Cancer	38.7	●	●		●		QoL
27	Del Fabbro 2010 (27)	Cohort	Hospital	USA	98	50	Cancer	IC	●	●			●	Symptoms
28	Del Fabbro 2011 (28)	Cohort	Hospital	USA	151	88	Cancer	IC	●					
29	Dijksterhuis 2021 (29)	Cohort	Hospital	Netherlands	406	82	Cancer - GI	48	●			●		
30	Dobs 2013 (30)	RCT	Hospital	USA and Argentina	159	81	Cancer - various	IC	●	●	●			
31	Durmaz 2020 (31)	Case control	Hospital	Turkey	62	86	Familial Mediterranean Fever	27.5	●	●	●		●	QoL, Symptom assess
32	Eagan 2012 (32)	Cohort	Hospital	Norway	408	75	COPD	30	●	●		●	●	
33	El Maghraoui 2016 (33)	Cross-sectional	Hospital	Morocco	134	75	Ankylosing spondylitis	11.9	●	●	●	●		
34	Elkan 2009 (34)	Cross-sectional	Hospital OP	Sweden	80	86	Rheumatoid arthritis	18.8	●	●		●		
35	Famil-Dardashti 2020 (35)	RCT	Hospital	Iran	47	69	Cancer - solid tumours	IC	●	●	●		●	QoL, Symptom assess

Lead author (year)		Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
36	Fogelman 2017 (36)	Cohort	Hospital	USA	89	69	Cancer - Pancreas	30.3	●				●	Symptoms
37	Fukushima 2019 (37)	Cross-sectional	Hospital OP	Japan	142	56	Cancer- Haematological	23.9	●	●	●			
38	Gabison 2010 (38)	Screening tool dev	Hospital OP	Israel	90	63	Cancer - various	58.9	●			●	●	Symptoms
39	Gale 2019 (39)	Cohort	Hospital OP	UK	50	50	Cancer - Thoracic and GI	IC	●	●	●			
40	Gannavarapu 2018 (40)	Cohort	Hospital	USA	3180	86	Cancer - Thoracic and GI	34.1	●					
41	Garcia 2013 (41)	RCT	Hospital	USA	18	82	Cancer	IC	●			●	●	Symptoms
42	Garcia 2015 (42)	RCT	Hospital	USA	82	50	Cancer	IC	●	●	●		●	QoL
43	Ge 2022 (43)	Case control	Hospital	China	262	69	Cancer - solid tumours	--	●	●	●		●	QoL, Symptom assess
44	Gingrich 2019 (44)	Cross-sectional	Hospital IP	Germany	100	56	Cancer and GI disease	32	●	●		●	●	
45	Glare 2011 (45)	Service evaluation	Hospital OP	USA	54	81	Cancer	IC	●		●	●		
46	Greig 2014 (46)	Phase I/II trial	Hospital OP	UK	13	63	Cancer	IC	●	●	●			QoL

	Lead author (year)	Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
47	Grundmann 2015 (47)	Pilot	Hospital OP	USA	7	63	Cancer - GI	IC	●	●		●		Performance status
48	Häne 2013 (48)	Screening tool dev	Hospital OP	UK	20	69	Cancer	IC	●					Symptoms
49	Helfenstein 2016 (49)	Cohort	Hospital OP	Switzerland	133	75	Cancer - various	15	●			●		
50	Hilal 2017 (50)	Cohort	Hospital OP	Germany	84	63	Cancer - Peritoneal, ovary & fallopian	22.6	●	●			●	
51	Horadagoda 2017 (51)	Cross-sectional	Hospital IP	Australia	94	56	COPD	23.4	●			●	●	
52	Hou 2022 (52)	Cohort	Hospital	Taiwan	232	38	Cancer - Pancreas	73.6	●	●			●	
53	Hugo 2016 (53)	Cross-sectional	Hospital OP	France	57	31	Rheumatoid arthritis	17.5	●	●	●	●	●	
54	Jouinot 2020 (54)	Cohort	Hospital OP	France	144	69	Cancer - Lung	--	●	●	●		●	
55	Kaduka 2017 (55)	Cross-sectional	Hospital OP	Kenya	512	69	Cancer	14.1	●	●		●		
56	Kamel 2020 (56)	RCT	Hospital OP	Egypt	40	88	Cancer - Pancreas	IC	●					
57	Kapoor 2017 (57)	RCT	Palliative care	India	63	64	Cancer	IC	●		●	●		QoL
58	Karmali 2017 (58)	Cohort	Hospital	USA	86	63	Cancer - Lymphoma	46.5	●	●		●		

Lead author (year)		Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
59	Katano 2021 (59)	Cohort	Hospital IP	Japan	416	56	CHF	10	●			●	●	
60	Kimura 2015 (60)	Cohort	Hospital	Japan	134	44	Cancer - Lung	45.6	●	●				
61	Kiriukova 2020 (61)	Cross-sectional	Hospital	Russia	60	63	Cancer - Pancreas	IC	●			●		QoL
62	Korousic Seljak 2020 (62)	Cross-sectional	Hospital IP	Slovenia	207	56	Cancer	66.7	●	●	●	●	●	
63	Kouchaki 2018 (63)	RCT	Hospital	Iran	90	44	Cancer - GI	IC	●		●		●	QoL
64	Kraft 2012 (64)	RCT	Hospital	Germany	72	56	Cancer - Pancreas	90.3	●	●		●	●	QoL
65	Kwan 2018 (65)	Cross-sectional	Hospital OP	UK	1755	63	COPD	4.6	●	●	●			
66	Lasheen 2010 (66)	Cohort (post hoc analysis)	Palliative care	USA	482	69	Cancer	31.1	●					Symptoms
67	Latenstein 2020 (67)	Cohort	Hospital	Netherlands	202	73	Cancer - Pancreas, bile duct, duodenum	71	●			●		
68	Lau 2018 (68)	Cohort	Hospital	USA	1366	77	Cancer - Lung	30.3	●					
69	Laviano 2020 (69)	RCT	Hospital	Croatia, Italy, Slovakia, and Sweden	55	69	Cancer - Lung	IC	●					

	Lead author (year)	Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
70	LeBlanc 2015 (70)	Cross-sectional	Hospital	USA	99	75	Cancer - Lung	32.9	●		●		●	
71	Lee 2010 (71)	Phase I/II trial	Hospital	South Korea	11	69	Cancer	IC	●	●		●	●	
72	Lemmey 2009 (72)	RCT	Hospital OP	UK	36	50	Rheumatoid arthritis	57.1	●	●	●		●	
73	Letilovic 2013a (73)	Cross-sectional	Hospital	Croatia	119	63	Malignant disease & CHF	35.3	●				●	
74	Letilovic 2013b (74)	Cross-sectional	Hospital IP	Croatia	137	50	Malignant disease & CHF	30.7	●	●	●	●	●	QoL, Symptoms
75	Liu 2021 (75)	RCT	Hospital	China	188	56	Cancer - Lung	--	●			●	●	
76	Loumaye 2015 (76)	Cross-sectional	Hospital	Belgium	152	68	Cancer - Lung & colorectal	48.7	●	●	●	●	●	
77	Loumaye 2017 (77)	Cohort	Hospital	Belgium	152	68	Cancer - Lung and colorectal	48	●	●	●	●	●	
78	Macciò 2012 (78)	RCT	Hospital	Italy	124	69	Cancer - Gynae	IC	●	●	●		●	Prognosis
79	Macleod Sandy 2013 (79)	Audit	Hospice care	New Zealand	40	44	Cancer - various	IC	●					Mood
80	Madeddu 2012 (80)	RCT	Hospital	Italy	60	38	Cancer	IC	●	●	●		●	Symptoms
81	Mahroug 2022 (81)	Cross-sectional	Hospital	Morocco	91	68	Rheumatoid arthritis	12.1	●	●		●		
82	Mantovani 2010a (82)	RCT	Hospital	Italy	332	38	Cancer	IC	●	●	●	●	●	Symptoms, QoL

Lead author (year)		Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
83	Mantovani 2010b (83)	Phase I/II	Hospital	Italy	24	81	Cancer - various	IC	●	●	●		●	Symptoms, QoL, Prognosis
84	Marchand 2022 (84)	Cohort	Hospital IP	Belgium	55345	63	All - excl psych and ICU	0.6	●			●		
85	Melenovsky 2013 (85)	Cross-sectional	Hospital	Czech Republic	408	91	CHF (NYHA I-IV)	19.1	●	●			●	
86	Minton 2012 (86)	Cohort	Various (Palliative, IP, OP & hospices)	Multicentre	1051	56	Cancer	24.7	●		●		●	QoL
87	Mohan 2017 (87)	Cross-sectional	Hospital	India	148	63	Cancer - Lung	20.9	●	●	●	●		
88	Mondello 2014 (88)	Cohort	Hospital	Italy	170	82	Cancer	IC	●				●	
89	Morikawa 2018 (89)	Cohort	Hospital IP	Japan	18	56	Cancer - Lung	61.1	●	●	●			
90	Morio 2021 (90)	Retrospective cohort	Hospital	Japan	79	31	Cancer - solid tumours	30.4	●	●		●		
91	Naito 2012 (91)	Cross-sectional	Hospital	Japan	47	31	Cancer	40.4	●				●	
92	Nemer 2017 (92)	Cohort	Hospital	USA	123	50	Cancer - Pancreas	71.5	●					
93	Ní Bhuachalla 2018 (93)	Cohort	Hospital OP	Ireland	725	81	Cancer - various	42.8	●	●		●	●	Anorexia / QoL

Lead author (year)		Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
94	Olsen 2020 (94)	cross-sectional	Hospital OP	Norway	71	69	RA, AS, & PsA	14.3	●	●	●	●		
95	Orell-Kotikangas 2017 (95)	Cross-sectional	Hospital OP	Finland	65	100	Cancer - Head & neck	30.8	●	●	●		●	
96	Ozorio 2017 (96)	Cross-sectional	Hospital	Brazil	101	63	Cancer - GI	63.4	●	●	●	●		
97	Paulo Araújo 2009 (97)	Case-control	Hospital OP	Brazil	66	50	CHF	IC	●	●			●	
98	Pelzer 2010 (98)	Cross-sectional	Hospital OP	Germany	65	81	Cancer - Pancreas	IC	●	●				
99	Petrusel 2019 (99)	Case control	Hospital	Romania	114	86	Cancer - Pancreas	19	●					
100	Pineda-Juárez 2018 (100)	Cross-sectional	Hospital OP	Mexico	224	38	Rheumatoid arthritis	51.8	●	●			●	
101	Powrózek 2018 (101)	Cohort	Hospital OP	Poland	70	44	Cancer - Head and neck	52.9	●			●	●	
102	Punzi 2012 (102)	Cross-sectional	Hospital OP	Italy	43	63	Cancer - Pancreas	65.1	●	●			●	
103	Radhakrishnan 2019 (103)	Cohort	Hospital	India	239	50	Cancer - Leukaemia	7.5	●					
104	Rasheedy 2021 (104)	Cross-sectional	Hospital IP	Egypt	206	63	Geriatric patients	13.6	●			●		
105	Rechinelli 2020 (105)	Cross-sectional	Hospital IP	Brazil	158	69	Cancer - solid tumours	36.1	●	●	●	●		
106	Riechelmann 2010 (106)	Phase I/II trial	Hospital OP	Canada	21	44	Cancer	IC	●	●				Anorexia / QoL

Lead author (year)		Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
107	Roeland 2017 (107)	Cross-sectional	Hospital OP	USA	36	69	Cancer - Colorectal	52.8	●	●				
108	Ruan 2021 (108)	Cohort	Hospital	China	746	56	Cancer - Lung and GI	IC	●	●	●	●	●	
109	Ruggeri 2020 (109)	Cohort	Palliative - community	Italy	969	50	Cancer - advanced	49.3	●		●	●	●	
110	Ryden 2008 (110)	Cross-sectional	Hospital	Sweden	28	44	Cancer - GI	46.4	●	●		●	●	
111	Sachlova 2014 (111)	Cohort	Hospital OP	Czech Republic	91	75	Cancer - GI	49.5	●			●	●	
112	Salsman 2015 (112)	RCT sub study	Hospital OP	USA	203	81	Cancer	IC	●	●	●	●		Symptoms, QoL
113	Sanchez-Rodriguez 2019 (113)	Cohort	Hospital	Spain	95	63	Geriatric patients	21.1	●	●		●		
114	Scheede-Bergdahl 2012 (114)	Cohort	Hospital	Canada	83	85	Cancer - Lung & GI	53	●	●	●	●	●	Symptoms, QoL
115	Silva 2020 (115)	Cohort	Hospital	Brazil	1166	75	Cancer - Colorectal	26.4	●	●		●	●	
116	Smiechowska 2010 (116)	Cross-sectional	Hospital	USA	70	75	Cancer - various	IC	●			●	●	Symptoms
117	Sobieszek 2021a (117)	Cross-sectional	Hospital	Poland	142	85	CHF	28.2	●	●		●	●	
118	Sobieszek 2021b (118)	Cross-sectional	Hospital	Poland	157	63	CHF	47.1	●	●		●	●	

Lead author (year)		Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
119	Solís-Martínez 2022 (119)	Cross-sectional	Hospital	Mexico	79	69	Cancer - H&N	72	●	●		●	●	
120	Srdic 2016 (120)	Cohort	Hospital	Croatia	100	75	Cancer - Lung	69	●	●			●	
121	Stäuber 2021 (121)	Observational	Hospital IP	Germany	175	94	Cancer - Prostate	20.3	●	●				
122	Stegel 2016 (122)	Cohort	Hospital	Slovenia	55	90	Cancer - Head & neck	14.5	●	●	●	●	●	
123	Stephens 2012 (123)	Cross-sectional	Hospital OP	UK	72	75	Cancer - GI	44.4	●	●			●	QoL
124	Sullivan 2018 (124)	Cross-sectional	Hospital	Ireland	1021	38	Cancer - GI	42						
125	Sun 2015 (125)	Cross-sectional	Hospital	China	390	81	Cancer - various	35.9	●	●				QoL
126	Suzuki 2020 (126)	Cohort	Hospital OP	Japan	128	75	CHF	14.4	●	●		●		
127	Szabó 2014 (127)	Cohort	Hospital	Germany	147	90	CHF (NYHA I-III)	16.2	●	●			●	
128	Szefel 2020 (128)	Case control	Hospital	Poland	158	50	Cancer - Colorectal	9	●	●		●	●	
129	Takayama 2016a (129)	Cohort	Hospital	Japan	406	69	Cancer - Lung	7.4	●	●	●		●	QoL
130	Takayama 2016b (130)	Phase I/II trial	Hospital	Japan	181	81	Cancer - Lung	IC	●	●	●		●	QoL

Lead author (year)		Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
131	Tavares 2022 (131)	Cohort	Hospital IP	Brazil	131	94	Chagas disease and HF	48.1	●	●	●		●	
132	Temel 2016 (132)	RCT	Hospital & community care	N. America, Europe and Australia	979	50	Cancer - Lung	IC	●	●	●		●	Symptoms
133	Thoresen 2012 (133)	Cohort	Hospital	Norway	50	69	Cancer - Colorectal	29.9/ 63.3/ 22.9	●	●		●	●	QoL
134	Thoresen 2013 (134)	Cohort	Hospital	Norway and Canada	77	56	Cancer	21.9/ 54.7	●	●		●	●	
135	Tobberup 2019 (135)	Cohort	Hospital	Denmark	52	69	Cancer - Lung	42.3	●	●	●	●	●	
136	Tumas 2020 (136)	RCT	Hospital	Lithuania	92	88	Cancer	44	●	●		●	●	
137	Turcott 2020 (137)	Cohort	Hospital	Mexico, Colombia, Chile	300	81	Cancer - Lung	--	●					
138	Vagnildhaug 2019 (138)	Cohort	Palliative care	Europe, Canada, Australia	628	69	Cancer	25	●					
139	van Bokhorst 2012 (139)	Cross-sectional	Hospital	Netherlands	103	81	Rheumatoid arthritis	1	●	●	●	●	●	Symptoms
140	Van Der Meij 2013	Cross-sectional	Hospital	Netherlands	40	75	Cancer - Lung	17.5	●	●	●	●		QoL

	Lead author (year)	Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
	(140)													
141	Vanhoutte 2016 (141)	Cohort	Hospital	Belgium	167	81	Cancer - various	17.9/ 49.7	●	●	●	●		QoL
142	Wallengren 2013 (142)	Cohort	Hospital	Sweden	405	81	Cancer - various	12 or 45/3 3/85	●	●	●	●		QoL
143	Weber 2009 (143)	Cross-sectional	Hospital OP	Germany	38	81	Cancer - GI	50	●	●				
144	Weryńska 2009 (144)	Cross-sectional	Hospital	Poland	40	88	Cancer - Lung	50	●	●			●	
145	Xie 2021 (145)	Cohort	Hospital	China	2364	44	Cancer	--	●	●	●	●	●	
146	Yeh 2013 (146)	RCT	Hospital	Taiwan	68	63	Cancer - Head & neck	IC	●					
147	Yennurajalingam 2012 (147)	RCT	Hospital	USA	31	81	Cancer - various	IC	●	●	●			
148	Yoon 2015 (148)	Feasibility	Hospital OP	USA	7	81	Cancer - GI	IC	●	●		●		Symptoms
149	Yoon 2020 (149)	RCT	Hospital OP	USA	30	95	Cancer - GI	IC	●	●			●	
150	Zhang 2021 (150)	Cohort	Hospital	China	2612	75	Cancer - solid tumours	IC	●	●			●	QoL
151	Zhou 2017a (151)	Screening tool development	Hospital	China	241	63	Cancer - various	49	●	●				QoL
152	Zhou 2017b (152)	Cross-sectional	Hospital	China	306	75	Cancer - various	30.4	●					

	Lead author (year)	Study design	Setting	Location	Study size	Quality score -%	Disease or condition	Cachexia prevalence (%)	Assessments made in studies:					
									Weight/ Height	*Body comp.*	*Physical function*	*Nutrition*	*Inflammatory markers*	*Other assessments*
153	Ziętarska 2017a (153)	Cross-sectional	Hospital	Poland	75	70	Cancer - Colorectal	0						
154	Ziętarska 2017b (154)	RCT	Hospital	Poland	114	63	Cancer – Colorectal	25.3	●			●		Symptoms, QoL
155	Zopf 2020 (155)	Cohort	Hospital	Germany	100	81	Cancer and non-cancer disease	41	●	●	●	●	●	

Assess: Assessment; *CHF:* chronic heart failure; *CP:* studies reported in conference proceedings; *COPD:* chronic obstructive pulmonary disease; *CRF*: chronic renal failure; *GI:* gastrointestinal; *H&N*: head and neck; *History*: clinical history or patient self-report; *IC:* inclusion criteria or 100%; *IP:* Inpatient; *MI*: myocardial infarction; *NYHA*: New York Heart Association functional classification; *OP:* Outpatient; *PC*: pre-cachexia; *QoL*: quality of life *RCT:* Randomised controlled trial; *Symptoms*: symptom burden, score or assessment

Appendix 11: Systematic Review Results Table 2

Table 2: Diagnostic criteria for cachexia referenced in the studies

Disease-associated with cachexia	Diagnostic criteria	Criteria details	Studies using these criteria
Ankylosing spondylitis	Evans 2008 (156)	WL ≥5% in the past 12 months AND underlying disease AND 3 of ↓muscle strength; anorexia; fatigue; low fat free mass index; abnormal biochemistry.	- El Maghraoui 2016
Chronic heart failure	Anker 1997 (157)	WL > 7.5% non-oedematous weight loss in last 6 + months	- Araújo 2011 - Paulo Araújo 2009
	Anker 1997 Anker 2003 (158) Evans 2008	*see above;* WL ≥5% AND abnormal biochemistry (C-reactive protein >5 mg/l or haemoglobin <120 g/l or albumin <32 g/l)	- Melenovsky 2013
	Evans 2008	*see above*	- Castillo-Martinez 2012 - Szabó 2014 - Suzuki 2020 - Sobieszek 2021a and b
	Fearon 2011 (159)	1. WL≥ 5% in 6 months OR 2. A BMI ≤ 20 kg/m² or and any WL > than 2%; OR 3. A skeletal muscle index (in the limbs) ≤ 7·26 kg/m² (males) and ≤ 5·45 kg/m² (females) and WL > 2%.	- Katano 2021
Chronic obstructive pulmonary disease	Schols 2005 (160)	BMI <21 kg/m² and a FFMI <16 kg/m² (men), <15kg/m² (women)	- Horadagoda 2017

Disease-associated with cachexia	Diagnostic criteria	Criteria details	Studies using these criteria
	Wagner 2008 (161)	FFMI < 17 kg/m² (men) and < 14 kg/m² (women) FFMI < 17 kg/m² for males and < t15 kg/m² for females (*unreferenced*)	- Eagan 2012 - Bahadir 2019
	European Respiratory Society Taskforce (Schols 2014) (162)	UWL >5% in 6 months and low FFMI (<17/15kgm-2)	- Kwan 2018
Rheumatoid arthritis	Baumgartner 1999 (163)	Relative skeletal muscle index ≤ 7.26 kg/m² (men)and ≤ 5.45 kg/m² (women)	- Lemmey 2009
	Evans 2008	*see above*	- van Bokhorst 2012
	Engvall 2008 (164)	FFMI< 10th percentile and with FMI >the 25th percentile	- Elkan 2009 - Hugo 2016 - Mahroug 2022
Cancer	partly based on Blackburn 1977 (165)	WL (>10% of pre-illness weight) and anorexia (of any severity)	- Lasheen 2010 (66)
	Fitzsimmons 1999 (166)	QLQ-PAN26 (moderate-severe loss of muscle strength and appetite scores)	- Bye 2013 (17)
	Ottery 1999 (167)	Symptom burden (PG-SGA) Nutrition status (PG-SGA)	- Andrew 2009 (6)
	Forrest 2003 (168)	Glasgow Prognosis Score	- Naito 2012 (91)
	Forest 2003 and McMillan 2013 (169)	Glasgow Prognosis Score	- Fukushima 2019 (37)

Disease-associated with cachexia	Diagnostic criteria	Criteria details	Studies using these criteria
	Fearon 2006 (170)	WL ≥ 10%, food intake ≤ 1,500 kcal/day, and systemic inflammation (CRP ≥ 10mg/L).	- Minton 2012 (86) - Sachlova 2014 (111)
	AIOM 2007 (171)	WL ≥ 5% in the last 6 months AND ↓muscle strength; Fatigue; Anorexia; Low lean mass index Biochemical changes: ↑ cytokine levels; Hb<12 mg/dl; Albumin < 3.2 mg kg^{-1}	- Punzi 2012 (102)
	Evans 2008 (156)	*see above*	- Buskermolen 2012 (16) - Castro 1019 (20) - Cavka 2022 (22) - Gingrich 2019 (44) - Korousic Seljak 2020 - Mondello 2014 (88) - Stephens 2012 (123) - Takayama 2016a (129)
	Bachman 2009 (9)	WL of ≥10% in 6 months	- Kraft 2012 (64)
	Bozzetti 2009 (14)	WL of ≥10% in 6 months	- Zietarska 2017a (153)
	Argiles 2017 (172)	CAchexia SCOre (CASCO)	- Bullock 2022 (15)
	Fearon 2011 (159)	1. WL≥ 5% in 6 months OR 2. A BMI ≤ 20 kg/m^2 or and any WL > than 2%; OR 3. A skeletal muscle index (in the limbs) ≤ 7·26 kg/m^2 (males) and ≤ 5·45 kg/m^2 (females) and WL > 2%.	- Álvaro Sanz 2019 (4) - Alvaro Sanz 2020 - Aredes 2018 - Atkas 2022 - Cavalcante Martins 2019 - Chen 2020 - da Rocha 2019 - de Clercq 2021

Disease-associated with cachexia	Diagnostic criteria	Criteria details	Studies using these criteria
			- Dijksterhuis 2021 - Daly 2016 - Debieuvre 2017 - Del Fabbro 2011 - Dobs 2013 - Gale 2018 - Gannavarapu 2018 - Garcia 2015 - Ge 2022 - Häne 2013 - Hou 2022 - Kaduka 2017 - Kamel 2020 - Kimura 2015 - Latenstein 2020 - Lau 2018 - LeBlanc 2014 - Loumaye 2015 - Mohan 2017 - Morikawa 2018 - Nemer 2017 - Ni Bhuachalla 2017 - Ozorio 2017 - Petrusel 2019 - Rechinelli 2020 - Ruan 2021 - Ruggeri 2020 - Solís-Martínez 2022 - Srdic 2016 - Stegel 2016 - Sun 2015 - Tobberup 2019 - Xie 2021

Disease-associated with cachexia	Diagnostic criteria	Criteria details	Studies using these criteria
			- Zhang 2021 - Zhou 2017a - Zhou 2017b
	Fearon 2011 (159)	see above and intake of <1500 Kcal/day	- Kapoor 2017
	Fearon 2006 and Fearon 2011	*see above*	- Thoresen 2012 - Thoresen 2013
	Douglas and MacMillan 2014 (173)	Modified Glasgow Prognosis Score	- Silva 2020
	Martin 2015 (174)	Grade 0–3 weight loss/low body mass index. *Adapted from Martin's BMI-adjusted weight loss grading system*	- Laviano 2020 - Turcott 2020
Cancer (contd.)	Muscaritoli 2010 (175), Fearon 2011 and Evans 2008	Muscaritoli (pre-cachexia): (1) WL 0-5% in 6 months; (2) Anorexia (either appetite <5 cm (VAS) or energy intake <70 of TEE); (3) Systemic inflammation (CRP ≥8 mg/l)	- Van Der Meij 2013
	Fearon 2006 (170), Evans 2008 (156) and Fearon 2011 (159)	*see above*	- Wallengren 2013
	Evans 2008 and Fearon 2011	*see above*	- Kouchaki 2018 - Vanhoutte 2016

Disease-associated with cachexia	Diagnostic criteria	Criteria details	Studies using these criteria
	Evans 2008 Bozzetti 2009 (14) and Fearon 2011	*see above*	- Zopf 2020
	Jafri 2015 (176)	CXI <49.8 Cachexia Index = [Skeletal muscle mass/ Albumin x Neutrophil-to-lymphocyte index]	- Karmali 2017
	Fearon 2011 and Cederholm 2017 (177)	WL ≥ 5%	- Powrózek 2018
Cancer and CHF	Evans 2008	*see above*	- Letilovic 2013
Cancer and non-cancer disease	Evans 2008 Bozzetti 2009 Fearon 2011	*see above* WL of ≥10% in 6 months See above	- Zopf 2020
Care of the elderly	Evans 2008	*See above*	- Rasheedy 2021 - Sanchez-Rodriguez 2019

BMI- Basal Metabolic Index; CRP C-reactive protein; CXI-Cachexia Index; FFMI fat free mass index; FMI fat mass index; Hb - haemoglobin; TEE - total energy expenditure; VAS - visual analogue scale; WL-weight loss

Appendix 12: Systematic Review Results Table 3

Table 3: Studies with pre-cachexia assessments

Lead author (year)	Study design / Setting	Disease / condition	Study size	Pre-cachexia prevalence - n (%)	Pre-cachexia diagnostic criteria
Aredes 2018	Cohort Hospital OP	Cancer - Cervical	49	3 (8.8%)	UWL ≤ 5% in last 6 months and anorexia ***(Fearon 2011)***
Atkas 2022	Cross-sectional Hospital	Cancer – solid tumours	200	40 (20%)	UWL ≤ 5% in last 6 months and anorexia ***(Fearon 2011)***
Bozzetti 2009	Cross-sectional Hospital	Cancer	1307	17% *(symptomatic)* 43% *(asymptomatic)*	UWL ≤ 10% - Symptomatic pre-cachexia (WL + anorexia, fatigue, early satiation) - Asymptomatic pre-cachexia (WL with none of the above features)
Cavalcante Martins 2019	Cohort (retrospective) Hospital IP	Cancer – Head & neck	97	28 (30.6%)	UWL ≤ 5% in last 6 months and anorexia or other metabolic disturbance ***(Fearon 2011)***
Gannavarapu 2018	Cohort Hospital	Cancer – thoracic	3180	116 (3.6%)	Minimal WL at time of cancer diagnosis: - UWL ≤ 5% for patients with a BMI ≥ 20 or - UWL ≤2% for patients with a BMI 20 ***(matched to Fearon 2011 by authors)***

Lead author (year)	Study design / Setting	Disease / condition	Study size	Pre-cachexia prevalence - n (%)	Pre-cachexia diagnostic criteria
Korousic Seljak 2020	Cross-sectional Hospital IP	Cancer	207	44 (21.4%)	Adapted a score from Evans 2008
Kwan 2018	Cross-sectional Hospital – outpatients	COPD	1755	28 (1.6%)	UWL >5% in last 6 months with normal FFMI ***(Schols et al, 2014)***
Ní Bhuachalla 2018	Cohort Hospital	Cancer-various	725	30 (5.8%)	Underlying chronic disease and; - UWL ≤ 5% in last 6 months; - chronic or recurrent systemic inflammatory response; - anorexia or anorexia-related symptoms. ***(Muscaritoli 2010)***
Ozorio 2017	Cross-sectional Hospital	Cancer - GI	101	11 (11%)	WL >5% in last 6 months w/o starvation ***(Fearon 2011)***
Ruggeri 2020	Cohort Palliative - community	Cancer - advanced	969	249 (25.7%)	UWL ≤ 5% in last 6 months and anorexia ***(Fearon 2011)***
Silva 2020	Cohort Hospital	Cancer - Colorectal	1166	45 (3.9%)	Modified Glasgow Prognostic Score (mGPS) ***(Douglas and MacMillan 2014)***
Solís-Martínez 2022	Cross-sectional	Cancer – Head & neck	79	8.8%	Pre-cachexia defined as WL >2% <5% ***(Fearon 2011)***

Lead author (year)	Study design / Setting	Disease / condition	Study size	Pre-cachexia prevalence - n (%)	Pre-cachexia diagnostic criteria
	Hospital				
Tobberup 2019	Cohort (retrospective) Hospital IP	Cancer - Lung	52	11 (21.2%)	Pre-cachexia defined as any WL ≤5% and presence of anorexia ***(Fearon 2011)***
Turcott 2020	Cohort Hospital	Cancer - Lung	300	91 (30.3%)	Pre-cachexia classified if patient is in the 1st risk grade (risk grade 0–1 [low risk] ***(Martin 2015)***
van Bokhorst 2012	Cross-sectional Hospital	Rheumatoid arthritis	103	1 (1%)	Underlying chronic disease and; -UWL ≤ 5% in last 6 months; -chronic or recurrent systemic inflammatory response; -anorexia or anorexia-related symptoms. ***(Muscaritoli 2010)***
Van Der Meij 2013	Cross-sectional Hospital	Cancer - Lung	40	9 (23%)	UWL ≤ 5% in last 6 months -Anorexia -Systemic inflammation ***(Muscaritoli 2010)***
Zhou 2017b	Cross-sectional Hospital	Cancer – Various	306	42 (13.7%)	UWL > 1kg and < 5% in past 6 months ***(Blum 2014)***
Ziętarska 2017	Cross-sectional Hospital	Cancer-Colorectal	75	56 (75%)	UWL <10% in last 6 months -No anorexia ***(Bozzetti 2009)***

Appendix 13: Systematic Review Results Table 4

Table 4: Assessments used in included studies

Anthropometric – weight/height	Weight (Kg) Weight/Height^2 for BMI	
Anthropometric - body composition	Skinfold assessment Upper and forearm circumference (arm muscle area) Leg circumference Waist circumference Calf circumference	BIA - Bioelectrical impedance analysis CT - computerised tomography scans DEXA - Dual-energy x-ray absorptiometry scans MRI - Magnetic resonance imaging scan PET - positron emission tomography Muscle tissue samples
Physical function	Handgrip strength Isometric knee extensor strength	Physical activity (step counter) 6MWT - 6-min walk test Laboratory-based exercise testing Physical activity survey: Indian Migration Study Physical Activity Questionnaire (IMS-PAQ) International Physical Activity Questionnaire (IPAQ)
Dietary/nutritional assessments	**Nutritional status:** CONUT - Controlling nutritional status score GNI – Geriatric Nutritional Risk Index MNA - Mini Nutritional Assessment MNA-SF – MNA Shor Form MST - Malnutrition Screening Tool MUST - Malnutrition Universal Screening Tool NRS 2002 - Nutritional Risk Screening tool 2002 PG-SGA - Patient Generated Subjective Global Assessment	**Dietary assessment:** 24-hour diet recall Food diary Dietary history interview DHD-FFQ Dutch Healthy Diet Food Frequency Questionnaire Indirect calorimetry, BMR and REE calculations

	SNAQ- Short Nutritional Assessment Questionnaire	
Laboratory tests	**Inflammatory and biomarkers:** CRP, HB and Albumin TNF-α, IL-1ß and IL-6 and CRP	**Other parameters:** Cholesterol profile, ProANP, resisitin, fasting glucose and insulin, ghrelin, prealbumin. leptin, adiponectin
Others	**Symptom assessment:** ASAS - Anderson Symptom Assessment Scale, based on ESAS CAS - Cachexia Assessment Scale ESAS - Edmonton Symptom Assessment Scale HADS - Hospital Anxiety and Depression Scale MDASI-J Japanese version of the M.D. Anderson Symptom Inventory MDASI - M.D. Anderson Symptom Inventory SCC - Symptoms and Concerns Checklist **Fatigue:** BFI - Brief Fatigue Inventory FACIT-F Functional Assessment for Chronic Illness Therapy–Fatigue	**Quality of life:** EQ-5D - EuroQol Group 5-Dimension Self-Report Questionnaire QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire QLQ-PAN26 scale for Patient with Pancreatic Cancer QOL-ACD Quality of Life Questionnaire for Cancer Patients Treated with Anti-Cancer Drugs **Appetite** BACRI-7 - Bristol-Myers Anorexia/Cachexia Recovery Instrument FAACT-ACS (Anorexia/CAX subscale of FAACT) MAF - Multidimensional Assessment of Fatigue SNAQ - Short Nutritional Assessment Questionnaire VAS Anorexia Score - Visual Analogue Scale

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Appendix 14: Baseline logistic regression models

Research Question 6: Logistic regression analysis of factors associated with significant documented weight loss

	Documented weight loss ≥ 5%	
	Odds Ratio (95% CI)	*P* value
Age at ICC appointment (years)	0.99 (0.94 - 1.05)	0.788
Socioeconomic deprivation, Index of Multiple Deprivation (IMD) quintiles		
1 (Most deprived)	ref	0.033*
2	2.46 (1.05 - 5.78)	0.039*
3	0.58 (0.17 - 2.00)	0.387
4 and 5 (Least deprived)	2.81 (0.99 - 8.02)	0.053
Living situation, n (%)		
Alone	ref	0.237
Spouse/partner	0.41 (0.17 - 1.00)	0.05
Other family	0.53 (0.10 - 2.82)	0.456
Other	0.48 (0.09 - 2.69)	0.404
Frailty, Rockwood Clinical Scale	1.25 (0.80 - 1.97)	0.329
Australia-modified Karnofsky Performance Status (AKPS)	0.99 (0.95 -1.02)	0.442
Mental capacity		
Yes	ref	ref
No	0.53 (0.11 - 2.50)	0.425
Health-related quality of life (EQ5D 5L)		
EQ5D utility score	0.68 (0.17 - 2.77)	0.589
Weight status, highest BMI in the previous year		
Underweight (BMI < 20 kg/m²)	ref	0.001*
Normal weight (BMI 20-24.9 kg/m²)	0.36 (0.11 - 1.17)	0.09
Overweight (BMI 25-29.9 kg/m²)	0.17 (0.05 - 0.56)	0.004*
Obese (BMI 30-39.9 kg/m²)	0.07 (0.02 - 0.26)	<0.001*
Severely obese (BMI > 40 kg/m²)	0.09 (0.01 - 0.76)	0.027*
IPOS – Loss of appetite score		
Not at all	ref	0.867
Slightly	1.08 (0.40 - 2.91)	0.88
Moderately	1.33 (0.49 - 3.62)	0.583
Severely and overwhelmingly	1.56 (0.49 - 4.98)	0.457

Research Question 8: Logistic regression analysis of factors are associated with a self-report of UWL in the previous 12 months

	Self-report of UWL	
	Odds Ratio (95% CI)	***P* value**
Sex, n (%)	2.37 (0.70- 8.06)	0.167
Socioeconomic deprivation, IMD quintiles		
1 (Most deprived)	ref	0.190
2	2..05 (0.72- 5.82)	0.176
3	0.58 (0.15 - 2.24)	0.427
4 and 5 (Least deprived)	0.50 (1.33 - 1.87)	0.301
Living situation, n (%)		
Alone	ref	0.016
Spouse/partner	1.93 (0.69 - 5.40)	0.212
Other family	0.96 (0.16 - 5.88)	0.967
Other	0.09 (0.02 - 0.49)	0.006
Frailty, Rockwood Clinical Scale	0.79 (0.52 - 1.21)	0.276
Health-related quality of life (EQ5D 5L)		
EQ5D utility score	0.49 (0.10 - 2.44)	0.381
Pre-ICC heaviest weight in past year	1.00 (0.95 - 1.07)	0.878
Pre-ICC highest BMI in past year	0.93 (0.74 - 1.18)	0.558
Pre-ICC weight loss - y/n	0.87 (0.30 - 2.56)	0.804
Pre-ICC WL over 5% - y/n	11.58 (3.68 - 36.42)	0.000
Weight status, highest BMI in the previous year		
Underweight (BMI < 20 kg/m²)	ref	0.080
Normal weight (BMI 20-24.9 kg/m²)	0.61 (0.10 - 3.87)	0.603
Overweight (BMI 25-29.9 kg/m²)	0.09 (0.01 - 1.04)	0.054
Obese (BMI 30-39.9 kg/m²)	0.07 (0.002 - 2.21)	0.133
Severely obese (BMI > 40 kg/m²)	0.07 (0.000 - 21.54)	0.364
IPOS – Loss of appetite score		
Not at all	ref	0.035
Slightly	1.33 (0.40 - 4.41)	0.644
Moderately	2.45 (0.79 - 7.56)	0.120
Severely and overwhelmingly	7.56 (1.85 - 30.87)	0.005

Research Question 14: Logistic regression analysis of factors associated with the management* of UWL, as documented in the primary care records of older patients

	Management action in the notes	
	Odds Ratio (95% CI)	***P* value**
Age at ICC appointment (years)	0.95 (0.88 - 1.04)	0.258
Socioeconomic deprivation, IMD quintiles		
1 (Most deprived)	ref	0.242
2	0.24 (0.06-0.95)	0.042
3	0.82 (0.20 - 3.40)	0.778
4 and 5 (Least deprived)	0.63 (0.14-2.78)	0.542
Living situation, n (%)		
Alone	ref	0.692
Spouse/partner	1.46 (0.69 - 5.40)	0.517
Other family	1.17 (0.16 - 5.88)	0.914
Other	3.15 (0.02 - 0.49)	0.289
Frailty, Rockwood Clinical Scale	0.72 (0.40 - 1.32)	0.293
Australia-modified Karnofsky Performance Status (AKPS)	0.96 (0.91 - 1.01)	0.079
Mental capacity		
Yes	ref	ref
No	4.58 (0.78 - 26.98)	0.093
Total no of comorbidities (ACE-27)	1.03 (0.81 - 1.32)	0.805
Health-related quality of life (EQ5D 5L)		
EQ5D utility score	0.94 (0.11 - 8.00)	0.957
EQ5D visual analogue	0.99 (0.96 - 1.02)	0.561
Pre-ICC heaviest weight in past year	0.94 (0.91 - 0.98)	<0.001
IPOS – Loss of appetite score		
Not at all	ref	0.075
Slightly	0.99 (0.29 - 3.42)	0.986

Moderately	1.06 (0.26 - 4.30)	*0.934*
Severely and overwhelmingly	9.88 (1.72 - 56.58)	*0.010*

**Management action is a composite measure of one or more of the following in the case notes - assessment / investigation / referral / treatment.*

Appendix 15: Initial qualitative data themes and sub-themes

INITIAL THEMES	Codes	Descriptions
Appetite loss	Nature of appetite loss	*Changes described - loss and return of appetite*
	Ageing and appetite	*Loss of appetite as a normal part of ageing*
	Changes in diet	*Patient experiences of making dietary changes in response to appetite loss.*
	Normalisation of appetite loss	*Perception that loss of appetite is not a concern due to acceptance of dietary changes or a perceived return of appetite.*
	Impact of stressful life events on appetite	*Role of life stressors e.g. bereavement, hospital admissions and other acute stressors.*
Health status, appetite and weight loss	Previous history of cancer or suspicion of cancer	*Previous history of cancer or mentions of cancer as a causative factor.*
	Complex medical history	*Patients' experiences of multimorbidity and polypharmacy that could be possible causes of weight loss (or loss of appetite).*
	Impact of diabetes as a chronic condition	*The impact of diabetes on perceived benefits of any weight loss (intentional or unintentional).*
	Memory loss	*Memory impairment that leads to the inability to recall weight loss timeframes or previous interactions with healthcare providers that may then lead to delays in assessment or investigation.*
	Health literacy	*Participants' understanding of medical conditions and how this may relate to weight loss*
Dietary habits	Current dietary and food preparation habits	*What participants eat, depending on their appetite and ability to prepare food, in a normal day.*
	Family dietary traditions/customs	*The role of childhood or family dietary habits and meal preparation on current eating habits.*
	Loss of enjoyment	*Loss of enjoyment in eating and preparing food and how this might contribute to weight loss*
Family and loved ones	Care giving	*Food preparation and input into maintaining a healthy diet.*
	Family and carer concern	*Concerns expressed by family caregivers and reactions to the weight loss (i.e., their input into seeking medical advice)*
Functional status	Muscle loss/wasting	*Perception of the effect of weight loss on the patient's physique and musculature.*
	Fatigue	*Fatigue that may be associated with loss of strength and weight loss.*
	Impact of weight loss on ADL	*How a loss of strength and function experienced by the patient affects their everyday life.*

Experiences of weight loss	Perceptions and the experience of unintentional weight loss	*Perceptions of weight loss and any concerns expressed by the participant.*
	Changes to appearance	Patient's perceptions of the impact of weight loss on their appearance.
	Intentional weight loss	*Weight loss that is or could be intentional despite the perceptions of the participant.*
	Reporting weight loss	*The factors that make a patient or caregiver seek medical attention for weight loss or mention their concern in a consultation.*
	Benefits of weight loss	*Expressed benefits of the weight loss as mentioned by the patient and or caregiver.*
	Speed/patterns of weight loss	*Temporal nature of the weight loss as noticed by patient and or caregiver*
	Potential causes of the weight loss	*Expressed causes or triggers for the weight loss by patient, family member and or caregiver.*
	Weight loss management	*Experiences of using prescribed or OTC supplementation as well as dietary changes to address the weight loss*
UWL in the overweight and obese	Experience of weight loss	*How weight loss - intentional, unintentional, weight fluctuations are perceived by those classed as overweight or obese.*
	Previous dietary habits or experiences of weight loss	*Dietary habits or experience of weight loss in childhood and middle age that contribute to an overweight or obese person's perception of unintentional weight loss.*
	HCP advice or response to weight loss	*Advice received or responses from healthcare professionals in consultations where weight loss concerns are mentioned by an overweight or obese person.*
Healthcare interactions	Primary Care	*Weight loss assessments or weight measurements conducted in primary care settings*
	Other healthcare settings	*Weight loss assessments or weight measurements conducted in other healthcare settings (ICC and beyond).*
	HCP advice or response to weight loss	*Healthcare professional responses to weight loss as reported by the patient or caregiver* - *Commentary or advice* - *Further referrals or investigations*
	Patient expectations of HCPs	*Expectations of how weight loss should be assessed or managed by HCPs when concern is expressed.*