The detection and assessment of malnutrition, sarcopenia and cachexia, in older adults with cancer

Alexandra Faye Bullock MNutr, RD

The University of Hull and the University of York

Hull York Medical School

May 2022

Abstract

Background: Older adults with cancer are a complex and growing population requiring tailored care to achieve optimum treatment outcomes. However, their care is complicated by under-recognised and under-treated nutrition-related wasting disorders: malnutrition, sarcopenia, and cachexia.

Aim: I aimed to understand better the prevalence, detection, assessment, and patients' experiences of malnutrition, sarcopenia, and cachexia in older adults with cancer.

Methods: I conducted three studies: i) a systematic review with narrative synthesis and meta-analysis investigating markers of malnutrition in older adults with cancer, ii) a systematic review with a qualitative synthesis investigating patients' views and experiences of malnutrition screening, and iii) a mixed-methods study screening for the three conditions, with concurrent qualitative interviews, to determine the feasibility of screening for, and the prevalence and overlap of, malnutrition, sarcopenia, and cachexia in a group of older adults with cancer, and to investigate patients' views and experiences of the conditions, and the screening processes. Interviews were thematically analysed through a phenomenological lens, with feedback loop analysis investigating relationships between themes. A modified critical interpretive synthesis was used to integrate overall thesis findings.

Findings: Review findings highlighted the homogeneity of markers of malnutrition in older adults with cancer. Decreased food intake and Prognostic Nutrition Index (PNI) were significantly associated with patient outcomes, but PNI, and other markers, could not distinguish between inflammatory or energy-deficient causes of weight loss. A lack of patient understanding of the causes and consequences of malnutrition was identified in the second review.

Mixed-methods quantitative data show malnutrition, sarcopenia, and cachexia to be highly prevalent, overlapping conditions, with more than one condition coexisting in 57%. Screening tools identified established disease rather than 'risk'. However, although common, nutritional and functional problems were often overlooked, overshadowed, and misunderstood by both patients and (in patients' perceptions) by clinicians; misattributed to ageing, cancer, or comorbidities. Patients viewed these conditions as both personal impossibilities, yet accepted inevitabilities.

Conclusion: Perceptions, identification, and management of these conditions needs to improve; with their importance recognised by clinicians and patients so those truly 'at risk' are identified whilst conditions are more remediable to interventions.

Table of contents

List of Tables and Figures

Tables

Figures

Acknowledgements

With never-ending thanks to my supervisors; to Professor Miriam Johnson for your constant support, and with my apologies for my appalling grammar. Dr Lewis Paton for your patience in explaining and answering so many statistics questions, and to Professor Mike Lind for your guidance. Thank you also to Professor Fliss Murtagh and Dr Maureen Twiddy for their invaluable advice and support.

I would also like to thank Yorkshire Cancer Research for funding the TRANSFORM project, and for all of the wonderful work they do to support those with cancer in Yorkshire. In particular, I would like to thank the TRANSFORM team; my fellow clinical researchers for their support as we traverse the PhD mountain: Mike (it's still better…), the 'other Alex' and the virtual office for the daily support, Sarah for encouraging me to start and keep up the running, and Cindy, my kind-of mentor, for so much. But mainly the Twinkies. As well as gaining so much knowledge I have been so lucky to work with such wonderful colleagues, and gain so many wonderful friends.

I would also like to extend a heartfelt thank you to the patients at Hull University Teaching Hospital NHS Trust, for giving up their valuable time to participate in this research. Thank you. Also thank you to the Trust R&D team, particularly Louise Hunn for her help and support, and excellent guidance when negotiating study pauses and restarts, and Dr Simon Stapley for his assistance during the last leg of recruitment.

Author 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. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull, or the University of York, regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised".

Publications, presentations, and prizes

Publications

Bullock, A.F., Greenley, S.L., McKenzie, G.A.G., Paton, L., Johnson, M.J. (2020) Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis, and meta-analysis. European Journal of Clinical Nutrition. 74: pp.1519-1535.

To date the article has been cited 45 times (Google /Web of Science citations: 45, 18.05.2022)

Bullock, A.F., Greenley, S.L., Patterson, M.J., McKenzie, G.A.G., Johnson, M.J. (2020) Patient, family and carers experiences of nutritional screening: a systematic review. Journal of Human Nutrition and Dietetics. 34(3): pp.595-603.

To date the article has been cited four times (Google /Web of Science citations: 4, 18.05.2022)

Prizes

Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis, and meta-analysis, top three in category prize winner, October 2020, European Association for Palliative Care

Patient, family and carers experiences of nutritional screening: a systematic review, prize winner; best presentation, May 2021, HYMS Postgraduate Research Conference, Hull

Invited speaker presentations

Patient, family and carers experiences of nutritional screening: a systematic review, May 2021, HYMS Postgraduate Research Conference, University of Hull

Detection and assessment of malnutrition, sarcopenia, and cachexia in older adults with cancer (from chapters four and seven), November 2021, UKRI-funded i3 Creating Connections Palliative Care Conference, University of Hull

Mixed-methods observational study explaining malnutrition, sarcopenia, and cachexia in older adults with cancer, April 2022, Joint Webinar: Cancer Prevention and Management SIG of ISBNPA, UK Society of Behavioural Medicine Cancer SIG, Physical Activity SIG of the Society of Behavioural Medicine, Online

Prevalence and overlap of malnutrition, sarcopenia, and cachexia in hospitalised older adults with cancer: a cross-sectional study, June 2022, Multinational Association of Supportive Care in Cancer, Annual meeting, Toronto, Canada

Poster presentations

Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis, and meta-analysis, October 2020, European Association for Palliative Care, Online

Prevalence and overlap of malnutrition, sarcopenia, and cachexia in hospitalised older adults with cancer: a cross-sectional study (from chapter seven), May 2022, European Association for Palliative Care, Online

Prevalence and overlap of malnutrition, sarcopenia, and cachexia in hospitalised older adults with cancer: a cross-sectional study, June 2022, Society on Sarcopenia, Cachexia and Wasting Disorders, Lisbon, Portugal

Chapter 1: Introduction

1.1 An introduction to the thesis

Older adults with cancer are a complex and growing population who require multi-layered care to achieve optimum anti-cancer treatment results (1, 2). The care of older adults with cancer is complicated by comorbidities and social factors associated with older age (2, 3). Despite this recognition, these are areas relatively overlooked in the field of oncology, but require consideration to enable the effective treatment of older adults with cancer.

Over the last 50 years, combined cancer mortality rates in the UK have decreased by 16%, reducing on average by 49% in people aged 74 and under (4). However, mortality rates in people aged 75 and over have increased by 15% (4), largely due to increasing incidences of cancer in the oldest old, and unequal access to anti-cancer treatments for older adults (1). Added barriers include fears around adverse effects of anti-cancer treatments (2), and other age-related factors including frailty, polypharmacy, cognition, and social support (5), which need to be considered to ensure the successful management of older adults with cancer.

There is an improving awareness of these cofactors in the management of older adults with cancer, but there is a further problem, common to older people, which is rarely discussed; a 'skeleton in the hospital closet', which will be the topic of this thesis. This 'skeleton' was first publicised by CE Butterworth in 1974, who highlighted a concern that 'so little attention has been paid to the essential role of good nutrition', with malnutrition remaining a cause of often preventable morbidity and mortality (6). This skeleton has been more recently described as the 'elephant in the room' in relation to its expanded definition to include the conditions of cachexia and sarcopenia; two disorders related to malnutrition, but with their own plethora of problems, both in relation to the clinical recognition and management of these conditions (7).

Malnutrition, sarcopenia, and cachexia are three conditions seen in varying degrees among the population of older adults with cancer, defined for this thesis as those aged 70 years or older. All three conditions are associated with poor tolerance of anti-cancer treatments, increased hospital lengths of stay, and poorer overall survival (8-11). Malnutrition is thought to affect between 20 and 85% of cancer patients, depending on cancer diagnosis (12). Similarly, sarcopenia and cachexia are thought to affect between 15-50% and 25-80% of cancer patients, respectively (13).

However, despite their prevalence and impact on patients, the identification, and subsequent treatment of these conditions is challenging. Although routine screening for malnutrition is recommended for all hospital patients (14), screening tools used to identify malnutrition risk

vary wildly in content and diagnostic rates. A study comparing three commonly used malnutrition screening tools in cancer patients found that malnutrition risk varied between 20 and 52%, depending on the tool used (15). Methods of screening for sarcopenia and cachexia exist, but they require multiple physical and blood measures and questions (16, 17), which can make them impractical to use in routine clinical practice.

Additionally, the clinical features of the three conditions overlap, making distinguishing between them problematic, for example, overall body weight loss is a key clinical feature of both cachexia and malnutrition, and loss of muscle mass is seen in all three conditions (8, 17, 18). However, the ability to distinguish one condition from another is required, as the medical treatment and management of each condition is different, ranging from intensive nutrition support and/or physical rehabilitation, to drug management and supportive care (14, 17, 19). For the purpose of this thesis, malnutrition, sarcopenia, and cachexia, although the terms may be used interchangeably in the literature, will be addressed as separate, distinguishable conditions. Although screening tools are designed to identify those at increased *risk* of a condition rather than making a diagnosis, for the purposes of this thesis, in places, tools which are designed to *screen* for the three conditions have been used to identify case positivity (discussed in section **3.4.8**).

In this chapter I will present a summary of cachexia, sarcopenia and malnutrition, introducing each in terms of its definition and proposed diagnostic criteria, as well as the implications of each of these conditions for older adults with cancer, and how these conditions are currently identified. This chapter will conclude with a review of the problems associated with the identification of the conditions, and how this thesis aims to address these issues.

This thesis aims to contribute to the knowledge base regarding these three under-recognised and undermanaged conditions, through optimising the detection and assessment of malnutrition, sarcopenia and cachexia in older adults with cancer, with the hope of adding some flesh to the elephant-sized skeleton in the closet.

1.2 An introduction to "Kakos hexis"; a bad condition

The first attempt to first define cachexia in cancer patients was made by Fearon et al., in 2006 (20). Although multiple clinical characteristics were associated with cachexia, including anorexia, weight loss, and fatigue, its 'complex, multifactorial origin' (20) meant defining, and therefore diagnosing cachexia in cancer patients was problematic (21). Weight loss, reduced oral food intake, and systematic inflammation were identified by Fearon et al., as the basic profile of cachexia, and some of the first evidence was provided suggesting cachexia was associated with survival (20).

A further attempt to define cachexia was made by Evans et al., 2008 (22), involving a consensus panel of clinicians and researchers. The agreed definition of cachexia was; *"a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass"*. Weight loss was identified as cachexia's prominent clinical feature, but anorexia, inflammation, insulin resistance, and muscle protein breakdown were recognised as important in cachexia's presentation. This definition marked cachexia as a wasting disease, distinct from other weight-losing disorders, *"distinct from starvation, age-related loss of muscle mass"* (22). Diagnostic criteria were also suggested: oedema free weight loss ≥5% in <12 months in the presence of underlying disease, or body mass index (BMI) <20kg/m^2 if weight loss is unknown (22). Meeting three of the following additional criteria were also required to diagnose cachexia; reduced muscle strength, fatigue, anorexia, low fat-free mass index, or abnormal biochemical markers (22). It must be highlighted that these were consensus criteria, as no validation work had been conducted at the time. It was acknowledged that cachexia's causes were complex and not fully understood, and a need to grade, or classify, cachexia, initially based upon the extent of weight loss, was suggested (22).

A position paper from special interest groups within the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2010, similarly defined cachexia as *"a multifactorial syndrome characterised by severe body weight, fat and muscle loss and increased protein catabolism due to underlying disease"* (23). To aid in staging cachexia, a definition for 'pre-cachexia' was included, containing four criteria; underlying chronic disease, a small unintentional weight loss of <5% body weight over six months, chronic or recurrent systematic inflammatory response, and anorexia or anorexia-related symptoms (23). It is noted that the methods for determining these definitions are not discussed, and the make-up of the special interest groups has not been described. Again, markers and their thresholds for cachexia and pre-cachexia are based on expert opinion.

Finally, an international consensus definition and classification for cancer cachexia was published by Fearon et al., in 2011, involving an expert panel of cancer cachexia researchers, oncologists, palliative medicine specialists and nutritionists (19). Two rounds of focus groups were conducted; to identify factors guiding clinical decision making in cachexia management, then reviewing cachexia statements and methods of assessment (19). Delphi rounds, developing cachexia classifications, were also conducted (19). The consensus definition produced for cancer cachexia was *"a multifactorial syndrome characterised 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. The pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism"* (19). It is important to note that this definition focuses solely upon cancer-specific cachexia, whereas previous definitions cover all diseases (19, 22, 23).

The international consensus definition expands on previous definitions, with the inclusion of cachexia's impact on function, and a description of its physiological processes (19). Limitations of the definitions were acknowledged, mainly the lack of assessment of psychological factors, the applicability of the diagnostic criteria to routine care, and the need to validate the work (19).

The definitions categorised cachexia into three stages, according to the degree of energy and protein depletion, in terms of energy stores (weight loss) and protein stores (BMI), and by their context for intervention (19). Pre-cachexia is identified with *"early clinical and metabolic signs, such as anorexia and impaired glucose tolerance" with* early multimodal interventions likely to be effective. End-stage, or refractory cachexia, is defined as *"clinically refractory as a result of very advanced cancer, or the presence of rapidly progressive cancer unresponsive to anti-cancer therapy"* with the stage of disease *"associated with active catabolism"*, characterised by a low performance score, or life expectancy under three months (19). These staging definitions provided the necessary language to communicate the clinical impact, and management, of cancer cachexia.

Although a small weight loss, such as >2%, may seem insignificant, a study, involving 8,160 cancer patients with locally advanced or metastatic cancers, found that a small weight loss, >2.4%, particularly with a low BMI, was predictive of poorer survival compared to patients with stable body weights, regardless of cancer diagnosis, stage or performance status (24).

At present, there is not a consensus regarding which is the most appropriate definition to use, and comparisons of the most commonly cited definitions show substantial variation in the

classification of cachexia; a study (25) of 167 cancer patients found that 40% of patients were cachexic according to Evans et al., 2008 definition, whereas 70% were classified as cachexic following the Fearon et al., 2011 definition.

Survival rates also varied by definition, with Evans et al., 2008 criteria associated with a shorter survival, compared to Fearon et al., 2011 criteria (0.55 years, versus 0.97 years respectively). It has been suggested that Fearon et al., 2011 criteria identifies cachexia in an earlier state, predicting a longer survival, and potentially enabling earlier targeted interventions. The inclusion of sarcopenia as a diagnostic criterion, plus a lower weight loss threshold, and lack of requirement of peripheral criteria, such as anaemia, could also be the cause of this (19, 22).

However, inclusion of measures of muscle loss can be seen as a starting point for the overlap between cachexia and sarcopenia (25). Studies reviewing the Fearon et al., 2011 criteria suggest inclusion of measures of skeletal muscle mass for cachexia, indicating sarcopenia may increase the estimated prevalence of cachexia in cancer populations, but consequently may reduce the ability of a diagnosis of cachexia to predict poorer patient outcomes (25, 26).

1.2.1 Clinical implications of cachexia

A comprehensive review of American and European literature found the prevalence of cancer cachexia ranged from 11 – 74%, depending on diagnosis (27); with gastric, head and neck, pancreatic, and lung cancer having estimated cachexia prevalence of 50 – 90%. This review also suggested cachexia prevalence correlates with estimated 5-year survival; diagnoses with a 5-year survival <30% having a higher risk of developing cachexia (80 – 90% chance), compared to diagnoses with a 5-year survival >91% (20 – 30% chance) (27).

As shown, cachexia is prevalent among cancer patients. However, it is also a condition that affects patients with other terminal diagnoses, including renal and heart failure, immunodeficiency virus, chronic obstructive pulmonary disease, degenerative diseases such as multiple sclerosis, and has been suggested to be a ‘nursing home’ condition, or a disease of ageing (28, 29). It is clear that cachexia is a common and wide-reaching condition. Although weight loss and inflammation are key diagnostic criteria for cachexia, other symptoms and consequences of cachexia are more systemic, involving multiple aetiologies, with wide-reaching implications, as proposed in **Table 1**.

A systematic review of cancer patients receiving palliative care, or diagnosed with advanced or metastatic cancer, estimated the prevalence of related systemic symptoms which are related to cachexia, finding 78% of patients reported fatigue, 42% reported anorexia, 32% reported a 5% weight loss and 19% a 10% weight loss (30).

Table 1: Symptoms and consequences of cachexia

Symptom or consequence of cachexia	Aetiology
Fatigue	**Physiological:** anaemia, inadequate nutrition, altered hypothalamic control of hunger, cytokine overproduction (31-33) **Endocrine hypofunction:** reduced cortisol production (34) **Psychological:** anxiety, depression, pain, reduced physical activity (31)
Anorexia	**Cytokines:** Tumour-Necrosis Factor (TNF)-α and Interleukin (IL)-6 associated with appetite suppression (28, 33) **Increased IL-6:** increases tryptophan, increases serotonin causing early satiety and hunger suppression (28) **Gastrointestinal symptoms:** nausea and vomiting, decreased gastrointestinal motility, constipation, obstruction (19) **Tumour:** release of pro-inflammatory cytokines (35) **Central nervous system:** alterations to neurotransmitters, neuropeptides, and prostaglandins, modulating appetite (35)
Weight loss	**Adipose loss:** increased lipolysis, reduced lipid uptake, reduced lipogenesis, starvation (36) **Muscle loss:** insulin resistance, reduced muscle synthesis, increased muscle breakdown, starvation, inflammation, reduced physical activity (28, 37) **Nutritional intake:** anorexia, fatigue, increased nutritional requirements (36, 37)
Physical function	**Cytokines:** activation of NF-κB reducing muscle synthesis, muscle proteolysis for production of acute phase proteins (28, 29) **Muscle wasting:** alterations to metabolic pathways, apoptosis activation and reduced regeneration (36) **Weight loss:** muscle weakness, reduced function, fatigue, inflammation (36, 37)
Quality of life (QOL) and social impact	Altered body image, altered eating habits, dependency, isolation, emotional distancing of carers, reduced physical activity (38-42)
Systematic inflammation	**Tumour progression:** activation of inflammatory response (36)

	Cytokines: including TNF-α, IL-6 are upregulated/activated, inflammatory mediators, secreted by immune cells or tumour (36) **Myostatin:** (GDF-8) inhibitor of skeletal muscle mass (43)
Anti-cancer therapies	**Chemotherapy:** may induce muscle loss, potential involvement of NF-κB, nutritional decline and weight loss, anorexia, nausea and vomiting (8, 44)
Reduced survival	Although cachexia is associated with mortality, the mechanisms are unclear. Possible mechanisms include; **Weight loss:** muscle and fat, inadequate nutrition **Thrombocytosis:** coronary symptoms or cardiac arrest **Compromised immunity:** increased risk of infection **Sarcopenia:** reduced skeletal, respiratory and cardiac function (25, 26, 45, 46)

1.2.2 Management of cancer cachexia

A detailed description of the management of cachexia is beyond the scope of this thesis, however a brief discussion of potential management strategies is presented.

Methods for managing and treating cancer cachexia are still in their infancy. Guidelines for the management of cancer cachexia, including the European Society for Medical Oncology (ESMO) (47) American Society of Clinical Oncology (ASCO) (48), and the ESPEN recommendations (12). Cachexia treatment requires multimodal approaches and patient-centred care (47, 48). Aspects of multimodal approaches for the management of cancer cachexia include; i) pharmacological interventions i) nutritional treatment, iii) exercise treatment, and iv) psychological and social support. Their aims of treatment, and current evidence for each are briefly discussed in **Table 2**.

Table 2: Current management strategies for cancer cachexia

Approach	Aim of treatment	Current evidence
Pharmacology	Manage tumour-associated inflammation. Counter wasting and hypercatabolism. Appetite stimulation. Endocrine therapies to alter hormonal regulation.	Pharmacological agents in development, include; Anamorelin, ghrelin receptor agonist to reduce muscle loss, and Enobosarm, selective androgen receptor modulator (49, 50) – no current recommendation for use. Corticosteroids and Progesterone analogues – moderate evidence for appetite improvement (48)
Nutritional treatment	Increase nutritional intake. Management of symptoms affecting intake, e.g. nausea and vomiting, obstructions. Nutritional screening and nutrition support	Dietary counselling; does not address metabolic aspects of weight loss. Dietary supplementation; lack of evidence of effect (48, 51, 52). Management of nutrition-impact symptoms e.g., nausea, anosmia, mucositis (47)
Exercise treatment	Preservation of muscle mass and function.	Exercise therapies to reduce inflammation, muscle degradation and loss; lack of evidence regarding efficacy and tolerance (40, 48, 52, 53).
Psychological support	Management of often neglected side effects affecting QOL; altered body image, social isolation, emotional impairment, education regarding cachexia	Improving awareness of impact of cachexia upon quality of life. quality of life assessment; no validated tool for cancer cachexia (39, 40, 52).

1.2.3 Identifying cancer cachexia

Despite developments in the definition, diagnostic criteria, and potential treatments for cachexia, the question of how to diagnose cachexia in clinical practice has so far received little attention. At present, two methods of screening for cachexia exist; the 'cachexia score' (CASCO) (54), and the 'cachexia staging score' (CSS) (55).

1.2.3.1 The CAchexia SCOre (CASCO)

The Cachexia Score, or 'CASCO' screening tool was developed to address the need to stage cachexia (22, 23, 54). Without the ability to stage, classify or track the progression of cachexia, management in clinical practice is not possible. The methodology used to produce CASCO is not detailed by the authors, other than stating Evans et al., 2008 and ESPEN, 2010, definitions were used (22, 23, 54). The CASCO tool includes 5 components; i) body weight loss and composition, ii) inflammation, iii) physical performance, iv) anorexia, and v) quality of life (54). **Table 3** details CASCO by symptom measured, its percentage weighting, measured parameter and threshold used (54).

CASCO has been validated, and refined to produce the Mini-Cachexia Score (MCASCO) (16). The validation study involved 186 cancer patients, with 95 age-matched, cancer-free controls. CASCO was applied, and psychometric analysis conducted determined the tool's reliability, construct, discriminant, and concurrent validity. CASCO correlated with other validated indexes, including the Eastern Cooperative Oncology Group (ECOG) score, and subjective diagnoses of cachexia by specialist oncologists (16). The simplified MCASCO was produced by streamlining CASCO whilst ensuring the psychometric properties remained. **Table 4** outlines MCASCO's content.

The CASCO tool development occurred before the publication of the international consensus criteria for cancer cachexia (19), therefore the tool is based upon cachexia definitions provided by Evans et al., and Muscaritoli et al., special interest group (22, 23). Before the international consensus, the terms 'pre-cachexia' and 'refractory cachexia' were not used, therefore CASCO uses 'mild, moderate, severe and terminal' to stage cachexia (54). At present, CASCO and MCASCO's ability to predict patient outcomes has not been validated, nor has its usability in clinical practice.

Table 3: Components of the CAchexia SCOre

Symptom	Percent	Measurement
Body weight loss and composition	40	Body weight loss Lean body mass
Inflammation, Metabolic disturbances, Immunosuppression	20	Inflammation – C-reactive protein (CRP). IL-6 Metabolic disturbances – Plasma albumin, pre-albumin, lactate, triglycerides. Anaemia. Plasma urea. Oxidative stress. Glucose tolerance test. Immunosuppression – IL2. Peripheral lymphocytes.
Physical performance	15	Total activity. Handgrip strength. Stair climb. 6-minute walk distance.
Anorexia	15	Simplified nutrition assessment questionnaire
Quality of life	10	Quality of life questionnaire

Adapted from Argilés et al., 2011, table 2: the CACHEXIA score (CASCO): a new tool for staging cachexia patients (54).

Table 4: Components of the Mini-CAchexia SCOre (MCASCO)

Component	Measurement
Weight	Body weight loss Lean body mass
Blood parameters	Inflammation – C-reactive protein Metabolic disturbances – Plasma albumin Immunosuppression – Absolute lymphocyte number
Questionnaires	Physical performance Anorexia Quality of life

Adapted from Argilés et al., 2017, table 5: MiniCASCO (16)

1.2.3.2 Cachexia Staging Score (CSS)

The CSS screening tool was produced to identify cachexia in clinical practice. The authors reasoned that although the MCASCO has been validated in clinical patients, the tool itself was not usable in clinical practice due to the large number of items and measures (55). To produce the CSS, 259 cancer patients datasets were analysed, alongside completed questionnaires of; the M.D Anderson symptom inventory (56), and the Functional Assessment of Anorexia Cachexia Therapy scale; a validated questionnaire evaluating QOL in cachexic patients (57). The SARC-F; sarcopenia screening tool (17), was completed, and performance status, using ECOG, and biochemical measures; white blood cell, haemoglobin, and albumin, were recorded (58). Finally, assessments of early satiety, taste and olfactory changes were made (55).

CSS components are detailed in section **1.2.3.3 .** Although the international consensus definition (19) was used to shape the CSS, it is noted that the methodology for developing the scoring system was not detailed (55). CSS validation by the authors compared stages of cachexia; no cachexia, pre-cachexia, cachexia, and refractory cachexia, against patient outcomes, and made comparisons between the five categories of the CSS by cachexia stage (55). This showed significant differences in survival between the four categories of cachexia (55). At present, no other study to validate the CSS has been conducted, nor has the clinical utility, or time to complete the CSS in clinical practice, been assessed. Despite the aim to produce a clinically useful tool, its acceptability in clinical practice has not been assessed.

1.2.3.3 Components of the Cachexia Staging Score (CSS)

- Weight loss in 6 months
- SARC-F (Sarcopenia screening tool (59))
- ECOG PS (Eastern cooperative oncology group performance status)
- Appetite loss, scored
- Abnormal biochemistry: white blood cell, albumin, haemoglobin) (55)

1.2.4 Gaps in the evidence

Although cachexia's evidence base is expanding, several key issues remain which require addressing.

1.2.4.1 The issues with definitions and diagnostic criteria

A number of attempts have been made to define cachexia (19, 20, 22, 23). Although the international consensus definition (19), developed specifically for cancer cachexia, is most commonly used, a debate remains regarding the appropriateness of this definition and criteria. The Evans et al., 2008 criteria, on which the international consensus definition is built, aims to identify cachexia in all diagnoses (19, 22), and includes additional supplementary criteria for

identifying cachexia (22). These criteria have arbitrary thresholds, produced by consensus, with assessment of validity ongoing (16, 25, 60). Arbitrary markers include percentage weight loss, BMI thresholds, levels of muscle loss, biochemical marker thresholds, and subjective markers such as fatigue and anorexia (19, 22, 23). Questions regarding the appropriate thresholds, and more importantly, the most appropriate markers for cachexia, need addressing, particularly in older adults with cancer, who are likely to have multiple morbidities, and treatment side effects, which may modulate these diagnostic criteria.

Another debate relates to the inclusion of sarcopenia as a diagnostic criterion by the international consensus, compared to the inclusion of decreased muscle strength and low fat-free body mass index by Evans et al., 2008 (19, 22). The requirement for a diagnosis of sarcopenia, or BMI <20kg/m^2, in conjunction with weight loss, places low skeletal muscle mass as an important marker of cachexia. However, it is unclear how useful including sarcopenia is in diagnosing cachexia (25, 61). This raises questions of, i) does inclusion of sarcopenia over-identify cachexia? (25), ii) is sarcopenia a condition that is indistinguishable from cachexia? (61), and, iii) due to their differing aetiologies and management, should other markers of muscle mass be used to diagnose loss of muscle mass in cachexia? (61).

1.2.4.2 The issues with screening for cachexia

Currently, two methods, with three screening tools; CASCO, MCASCO, and CSS, have been produced to identify cancer cachexia. The CASCO screening tool performed well against the international consensus diagnostic criteria for identifying cachexia (18), and has been validated in a small population (16). However, the clinical utility of the tool, which includes 34 questions, 11 biochemical markers, and two anthropometric markers, has not been assessed. The condensed version, MCASCO, is significantly shorter, with 15 questions, four biochemical markers and two anthropometric markers (16). The MCASCO was shown to contain the psychometric properties of CASCO in statistical tests, nevertheless, its clinical utility, like CASCO, has not been established (16, 54). The CSS was produced due to the concerns regarding the length, and clinical utility of the CASCO (55). CSS includes two questions regarding weight and appetite, five questions to complete the SARC-F, and three biochemical markers (17, 55). Although the CSS is shorter, it requires assessment of physical performance by clinicians, and the SARC-F questionnaire only identifies patients with probable sarcopenia, with further assessment required to diagnose sarcopenia (17, 59). The clinical utility of CSS has also not been assessed, and it has only been validated in one small population, with its ability to discriminate between the four stages of cachexia against key clinical outcomes currently being conducted (55).

As with the diagnostic criteria, thresholds and markers of cachexia in the screening tools are arbitrary, and require further investigation (16, 25, 55).

Another issue, not addressed within the screening tools, nor the definitions, is the apparent overlap of cachexia with malnutrition. In all proposed definitions, diagnostic criteria and screening tools, weight loss is relied upon to diagnose cachexia (16, 19, 22, 55). However, weight loss is also the key diagnostic criteria for malnutrition (62), a condition prevalent in older adults with cancer (12). Additionally, the inclusion of sarcopenia within the CSS, and measures of muscle mass in CASCO and MCASCO overlap the diagnostic criteria for cachexia with sarcopenia, questioning whether sarcopenia is a contributing factor to cachexia, or if it is a separate condition.

These points raise questions regarding the current ability to screen for cachexia in clinical practice, as well as the validity of the measures themselves for identifying cachexia, rather than other wasting conditions. Combined, these issues highlight a need for a shorter, clinically relevant, and well-validated method of screening for cachexia, which takes into account the probability of other conditions, such as sarcopenia and malnutrition, which are likely to be prevalent in an ageing population. Also, further investigation of the validity of cachexia's markers, and their appropriate thresholds, is required.

To produce a validated screening tool, considerations of the tool's face and content validity, as well as discriminant validity, and ability to predict relevant clinical outcomes, are essential (14, 63). Finally, consideration of the tool's feasibility, applicability and usability in clinical practice is essential when developing methods for screening in clinical settings (14, 63).

1.3 An introduction to “Sarx penia”; flesh loss

The term ‘sarcopenia’ was initially posed by Rosenberg in 1989 to describe the age-related loss of muscle mass (64, 65). As with cachexia, the development of a definition for sarcopenia evolved from numerous working groups, but to a greater extent. Therefore, six key definitions, which include both measures of function, and body composition variables, that have influenced the development of sarcopenia screening tools, will be covered in this review.

Initially, the European Working Group on Sarcopenia in Older People (EWGSOP), aimed to answer; what is sarcopenia, what parameters define it, what variables, which tools, and what thresholds will be used to measure sarcopenia, and how does sarcopenia relate to other conditions? (59). They defined sarcopenia as *“a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death”* (59). EWGSOP recommended diagnosis based on; low muscle mass, and, either low muscle strength or low physical performance (59), justifying that muscle strength does not solely depend on muscle mass (66). EWGSOP recognised the overlap between sarcopenia and other wasting conditions, including cachexia and frailty, encouraging differentiation between these conditions due to their differing aetiologies and management therapies (59). EWGSOP also suggested potential diagnostic tools to measure muscle mass, strength, and function, which included body imaging techniques, bioimpedance analysis, anthropometric measures, and physical performance tests (59). Possible thresholds for sarcopenia diagnosis were suggested, but not defined (59). This consensus proved a pivotal milestone in the journey to define sarcopenia.

Soon after, the International Working Group on Sarcopenia (IWGS) (67) suggested diagnostic criteria, and provided thresholds for measures based on gait speed and muscle mass. The methodology for the development of these criteria was not presented, except in reference to thresholds for appendicular lean mass, as sex-specific thresholds for the lowest 20% of the distribution, in a study comparing two definitions of sarcopenia in older adults (aged 70 to 79 years) (68).

At this time, the Society of Sarcopenia, Cachexia and Wasting Disorders (SSCWD) (69), also produced an international consensus, introducing a definition and diagnostic criteria for ‘sarcopenia with limited mobility’, as *“as a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-minute walk, and who has a lean appendicular mass corrected for height squared of 2 standard deviations or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group”.* The Asian Working Group (AWGS) for Sarcopenia subsequently provided defined thresholds for

Asia, and agreed with the EWGSOPs definition of sarcopenia (59, 70). It is interesting to note, that no group documented, discussed or justified their methodologies used, or the composition of their working groups.

In 2014, the Foundation for the National Institutes for Health (FNIH), a collaboration between public and private institutions, published the FNIH Sarcopenia project (71). FNIH aimed to define clinically relevant thresholds for weakness and low muscle mass, determine their predictive ability, and compare their criteria against previous diagnostic criteria for sarcopenia (71). This study, involving 26,625 older adults, produced diagnostic thresholds for hand-grip strength and appendicular lean mass, adjusted for BMI, for sarcopenia (71).

Finally, EWGSOP published a revised consensus definition and diagnosis in 2019, known as EWGSOP2 (17), to reflect advances in research, and consolidate evidence gained in the decade since the original guidelines were produced. In these, an updated definition of sarcopenia was proposed as a *"progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality"* (17). Alongside this, diagnostic criteria were altered to reverse the positions of muscle strength and mass, highlighting the change in opinion that muscle strength, rather than muscle mass, is more predictive of patient outcomes (17). EWGSOP2 also provided guidelines on validated measures and screening tools for sarcopenia (17). Processes used for the production of these updated guidelines are well justified in the report.

As with cachexia, estimations of the prevalence of sarcopenia vary depending on the diagnostic criteria used (72). Comparison of the EWGSOP 2010 and EWGSOP2 criteria have found that the prevalence of sarcopenia decreased by an average of 7% when using the EWGSOP2 criteria, compared to EWGSOP1 (17.7% vs 11%) in community-dwelling older adults (73). During the FNIH study (72), the EWGSOP 2010, FNIH thresholds and IWGS criteria were compared in 10,063 participants aged 65 and older. They found a prevalence of 1.3% in men and 2.3% in women using the FNIH criteria, 5.1% and 11.8% in men and women respectively using the IWGS criteria, and 5.3% and 13.3% in men and women respectively using EWGSOP 2010 criteria (59, 67, 74). Similarly, a review of the general population, using the EWGSOP 2010, IWGS and AWGS criteria found an overall prevalence of sarcopenia of 10% in both men and women (75). However, when considering older adults with chronic diseases, the estimated prevalence of sarcopenia is higher. A systematic review of 18 studies with patients aged 50 years or older, using EWGSOP 2010 criteria, prevalence of sarcopenia was 1 – 29% in community-dwelling, and 14 – 33% in long-term care patients (76). More specifically, a systematic review of sarcopenia in pre-therapeutic cancer patients found an average

prevalence of 38.6%, with oesophageal and small-cell lung cancers showing the highest prevalence of sarcopenia, of 44 – 79% and 75% respectively (77).

1.3.1 Mechanisms of sarcopenia

In understanding sarcopenia, the mechanisms and risk factors for sarcopenia's development must be explored. For this, concepts of 'primary sarcopenia' and 'secondary sarcopenia' require discussion. 'Primary' refers to age-related sarcopenia, where no other specific cause is apparent, whereas 'secondary' indicates sarcopenia caused by systemic disease, particularly a disease which promotes inflammation (17). Other factors, such as lack of physical activity, or inadequate dietary calorie and protein intake, can also be contributory (17). The EWGSOP2 guideline suggests sarcopenia can be further categorised as 'acute' or 'chronic', with acute lasting less than six months, related to an acute illness or injury, and chronic, lasting more than six months, associated with progressive or chronic conditions (17). These additional classifications aim to encourage the identification of sarcopenia's aetiology, enabling more appropriate interventions and treatments (17). Mechanisms of age-related sarcopenia are not fully understood, with those thought to be involved shown in **Table 5**.

Table 5: Potential mechanisms in the development of age-related sarcopenia

Suspected mechanism	Aetiology
Neuromuscular degeneration	Atrophy of muscle fibres; particularly type II, fast-twitch fibres, decrease in alpha motor units from spinal cord, intra-muscular fat infiltration (myosteatosis), imbalance in protein metabolism, reduction of satellite cells (78, 79).
Hormonal changes	Reduced growth hormone (GH), IGF-1 (increased visceral fat, reduced lean body mass), testosterone and DHEA (80).
Insulin resistance	Anabolic resistance leading to muscle loss; particularly in sarcopenic obesity. Insulin resistance in skeletal muscle, associated with aging. Insulin acts as a satiety hormone (81-83).
Inflammation	Increased inflammatory markers with age; TNF, IL-6, IL-1, C-reactive protein and low-grade inflammation (78, 81).
Sedentary lifestyle	Sedentary lifestyle, bed rest; immobility, deconditioning (80).
Dietary intake	Reduced protein and energy intake, micronutrient deficiency, malabsorption, anorexia, declining intake with age (80, 83).
Anorexia	Decreased dietary intake, declining muscle mass. Reduced hunger; reduced ghrelin and Neuropeptide Y, increased leptin, insulin, peptide YY, early satiety (83).
Obesity	Sarcopenic obesity; reduced lean body mass with excess adiposity; fat infiltration into muscle, reduced physical function, insulin resistance (80).

1.3.2 Clinical implications of sarcopenia

Sarcopenia is particularly prevalent in older adults with cancer; with sarcopenia affecting an estimated 38.6% of older adults with cancer (77), however, sarcopenia's impact is not well recognised. In hospitalised patients, sarcopenia is associated with increased length of stay, increased risk of readmission, and an increased risk of hospital-acquired infections (84, 85). It has been suggested that sarcopenia is the cause of 1.5% of total healthcare costs in the United States (86). This was estimated using stringent criteria, similar to FNIH (71), therefore estimates may be modest. Assuming similar UK figures, a 1% cost represents a predicted expenditure of £1.43 billion in health costs in 2020/21 in England alone (86, 87). In addition to financial costs, sarcopenia is independently associated with mortality, both in older patients (88), and cancer patients, including increasing risk of mortality in pancreatic cancer patients by 71% (89), and all cancer types by 51% (90). Low skeletal muscle mass is also a predictor of surgical complication and prognosis for patients receiving surgery for head and neck cancer (91). Regardless of cancer diagnosis, sarcopenia is also associated with an increased number of severe chemotherapy toxicity events, at nearly four times the risk (10). Sarcopenia has also been associated with cognitive impairment in older adults, with a systematic review finding that, on average, cognitive impairment was found in 40% of sarcopenic patients, compared with 23% of non-sarcopenic patients (92), although it is noted that causality cannot be determined from these observational data. Finally, diagnostic criteria for sarcopenia, including slow gait speed and low hand-grip strength, have been shown to be related to an increased risk of activities of daily living (ADLs) disability, including disability to bathe, dress or feed (93).

1.3.3 Sarcopenia and pharmacokinetics

Due to age-related changes in body composition, including increased lipogenesis and reduced myogenesis, combined with lipid infiltration of skeletal muscles, and redistribution of lipid stores increasing visceral fat (94, 95), another aspect of the impact of sarcopenia upon older adults must be considered. These body composition changes, of a relative increase in body fat, and progressive reduction in total body water and lean mass, can alter pharmacodynamics, which is of particular concern for older adults with cancer (96).

Depending on a drug's mechanism; of either hydrophilic (water-soluble) or lipophilic (fat-soluble) medications, drug volume distribution can be altered depending on body composition (96). Individuals with a higher fat mass, and lower muscle mass, such as those with sarcopenia, may be at an increased risk of toxicity from lipid-soluble medications, due to an increased volume of distribution and subsequent increased half-life (96, 97).

This is of particular issue when considering older adults with cancer, where lower lean body mass and higher fat mass have both been seen to be predictors of chemotherapy toxicity (98). These predictors of toxicity are seen independently of BMI (99, 100).

It has also been suggested that cachexic patients are at similar risk due to these mechanisms, where a loss of both fat and lean muscle mass alter both hydrophilic and lipophilic drug distribution and metabolism (101). From this, it has been suggested that medication doses, including anticancer treatments, may need to be moderated depending upon patient body composition (101).

1.3.4 Management of sarcopenia

A detailed description of the management of sarcopenia is beyond the scope of this thesis, however, a brief outline, adapted from guidance published by the International Conference on Sarcopenia and Frailty Research (ICFSR) taskforce, is detailed (102). Structured evaluation of the literature, drawing on international consensus statements, systematic reviews, and a multidisciplinary and global task force, were used to produce evidence-based guidelines for sarcopenia in older adults aged 65 and older (102). Evidence quality is ranked by overall certainty of the evidence, from very low, to low, moderate, and high. Recommendations for the management of sarcopenia are shown in **Table 6.**

Table 6: International clinical practice guidelines for sarcopenia; management of sarcopenia

Strategy	**Guideline**	**Certainty of Evidence**
Physical activity	**Resistance-based training;** to improve lean mass, strength and physical function	Moderate
Protein	**Protein supplementation;** consideration of protein supplementation/protein-rich diet	Low
	Discussion of importance of adequate caloric and protein intake	Very low
	Combination of nutritional (protein) and physical activity intervention	Low
Vitamin D	Insufficient evidence	Very low
Anabolic Hormones	Insufficient evidence	Very low
Pharmacological intervention	Not recommended as first-line therapy	Very low

Adapted from: Dent et al., 2018: Clinical Practice Guidelines for Older People with Sarcopenia (102).

1.3.5 Identifying sarcopenia

As shown, understanding of sarcopenia's mechanisms and treatment is progressing, aided by developing consensus definitions of the condition. Alongside this, methods to screen patients for sarcopenia have also been developed. At present, four main tools for the detection of sarcopenia exist, and are detailed;

1.3.5.1 Short Portable Sarcopenia Measure (SPSM)

The aim of the SPSM, produced in 2009, was to combine estimates of muscle quality and function in one scale, using easily obtainable measures which do not require sex-specific adjustments, and can track changes in muscle status over time (103). The tool was developed with 998 African American participants, aged 49-65 at baseline, with follow-up completed at 36 months. Measures include timed chair rises, lean mass, and grip strength divided by height (103). Construct validity of the tool was performed using the original population; SPSM correlated with physical performance measures, but had weaker associations with body composition measures (103).

1.3.5.2 The Ishii formula

The Ishii Formula was developed in 2014 with 1,971 community-dwelling older adults, aged 65 and older, in Japan, who were functionally independent (104). The formula followed recommendations provided by EWGSOP 2010 regarding diagnostic criteria for sarcopenia, and uses age, calf circumference (CC) and handgrip strength (HS), to produce a score (104);

Men: 0.62 x (age-64) – 3.09 x (HS – 50) – 4.64 x (CC – 42)
Women: 0.80 x (age x 64) – 5.09 (HS – 34) – 3.28 x (CC – 42)

The formula has been validated in 380 Chinese hospital inpatients, aged 60 and over, finding sarcopenia was an independent predictor of three-year all-cause mortality (105). Similarly, a study of 280 Caucasian adults, aged 65 and older, found sarcopenia was associated with worse functional status, and ability to walk at hospital discharge (106). As the EWGSOP guidelines have been updated (17), placing increased diagnostic weighting on muscle strength, the formula does not correspond with sarcopenia's most up-to-date diagnostic criteria.

1.3.5.3 Mini Sarcopenia Risk Assessment (MSRA) questionnaire

The MSRA was developed in 2017 and is based on EWGSOP 2010 diagnostic criteria, and includes seven questions, of physical and nutritional characteristics related to sarcopenia; age, protein intake, dairy intake, daily number of meals, physical activity levels, number of hospitalisation in a year, and weight loss in the last year (107). A five-question version of MSRA, showing marginally improved sensitivity and specificity (108), has been validated.

1.3.5.4 SARC-F questionnaire

The SARC-F was developed in 2013 as a rapid diagnostic test for sarcopenia, comprising of five components; strength, assistance walking, rise from a chair, climbing stairs, and falls, scored according to the severity of each component (109). SARC-F has been validated in multiple studies (110, 111), including the Baltimore Longitudinal Study of Aging, and the National Health and Nutrition Examination study (110), finding a score of ≥4 was associated with ADL deficits, increased risk of hospitalisation, and of mortality. A prospective cohort study (112), involving 4000 participants, comparing SARC-F against consensus definitions of sarcopenia; EWGSOP, IWGS, and AWGS, found SARC-F had a specificity of 94-99%, however, sensitivity was low, at 4 to 10%; suggesting it is highly accurate in identifying actual cases of sarcopenia, but has a high false-positive rate.

Several iterations, modifications, and extensions of the SARC-F screening tool have been posed, and include a three-item version of the SARC-F published in 2018 (113), the SARC-F Algorithm in 2019 (17), SARC-CalF first posed in 2016 (114), and SarSA-Mod in 2021 (115). To develop the three-item version of SARC-F (113) the predictive ability of each component of the original five-item tool was determined, using a population of 4000 community-dwelling older adults (113), with strength, climbing stairs, and assistance walking, identified as most predictive of sarcopenia. However, the sensitivity and overall diagnostic accuracy of the three-item tool has been suggested to be poorer than the five-item SARC-F, making the three-item too currently unsuitable for use in diagnosing sarcopenia (116).

The updated EWGSOP2 guidelines (17) included an algorithm for diagnosing and quantifying the severity of sarcopenia in clinical practice, which may aid with rectifying the poor specificity of the SARC-F questionnaire. The updated guideline also includes thresholds for measures that identify and characterise sarcopenia, including sex-specific cut-offs for handgrip strength, chair stand test, gait speed, timed up and go, and appendicular skeletal muscle mass (17). However, they acknowledge that some thresholds remain arbitrary, with further research required to determine appropriate thresholds, and their predictive values. **Figure 1** details the algorithm for case-finding, making a diagnosis and quantifying the severity of sarcopenia in practice.

Further iterations and methods of detecting sarcopenia have been posed, and include modified versions of the SARC-F; of the SARC-CalF (114)and SarSA-Mod (115), which include additional components, e.g., anthropometric measures, to increase the diagnostic accuracy of the original SARC-F tool, or the Goodman et al., screening grid (117) which presented a predictive model for sarcopenia, and Yu et al., (118) who developed predictive equations for sarcopenia. However, the validity and efficacy of these tools are variable (119, 120).

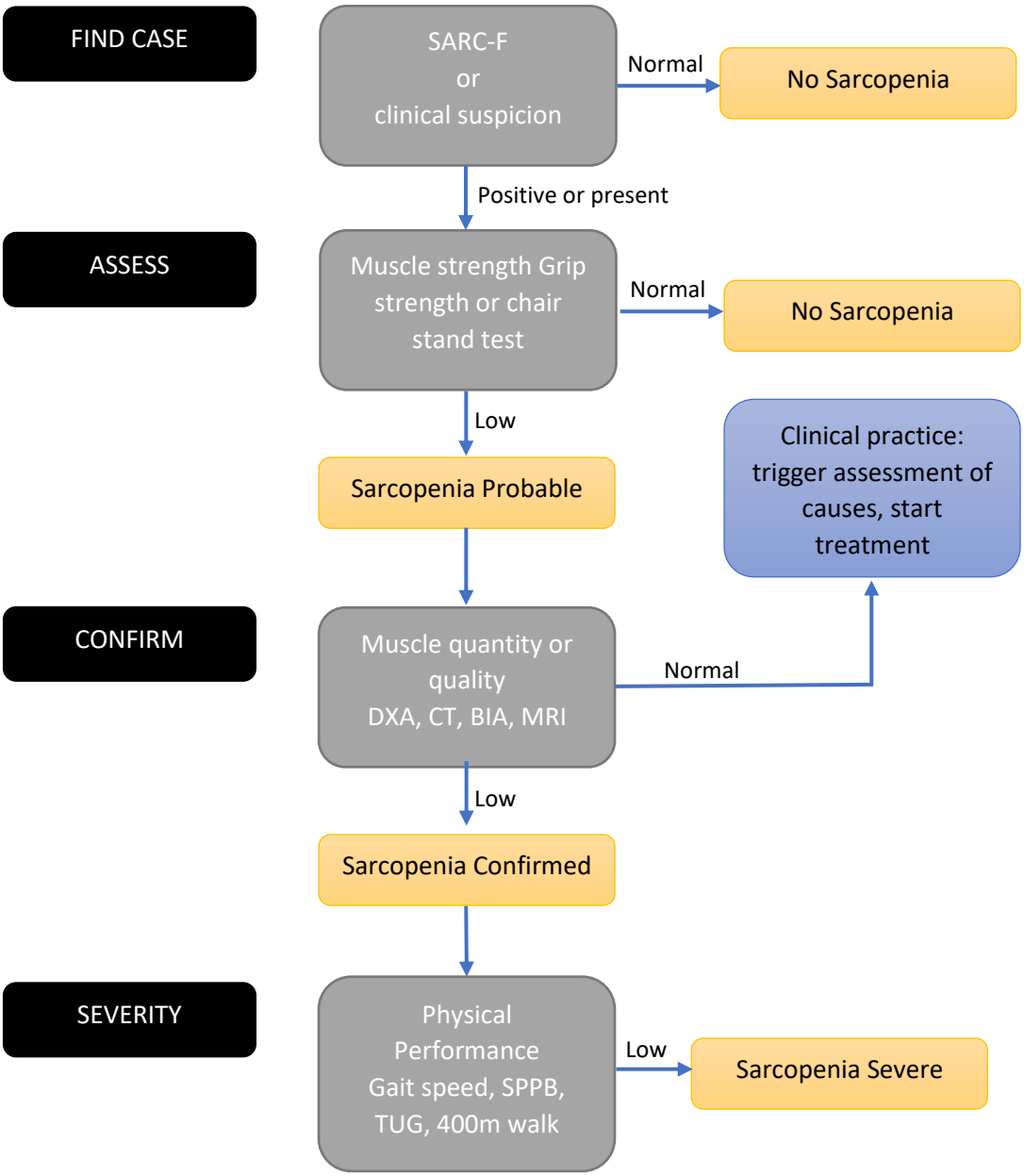


Figure 1: European Working Group on Sarcopenia in Older People 2; Algorithm for case-finding, making a diagnosis and quantifying severity of sarcopenia in practice

Adapted from Cruz-Jentoft et al., 2019, figure 1; Sarcopenia: EWGSOP 2 algorithm for case-finding, making a diagnosis and quantifying severity in practice (17).

Key: DXA – Dual X-ray absorptiometry, CT – Computer tomography, BIA – Bioelectrical impedance analysis, MRI – Magnetic resonance imaging, SPPB – Short physical performance battery, TUG – Timed up and go test.

1.3.6 Gaps in the evidence

As previously discussed, many published working definitions for sarcopenia exist (17, 67, 69, 121), however, there remains a lack of an agreed definition or diagnostic criteria. With this, the estimated prevalence of sarcopenia varies by definition and criteria used (72, 73), and a lack of consensus makes implementation of regular screening for sarcopenia in clinical practice challenging.

A study comparing the five most commonly used screening tools for sarcopenia, against five diagnostic definitions of sarcopenia, was conducted in 306 community-dwelling participants (119). The study found that the prevalence of sarcopenia varied depending on the definition used, between 5.7% (AWGS) (70) and 16.7% (EWGSOP) (59). Results showed only slight to moderate agreement across diagnostic definitions; except between EWGSOP 2010 and IWGS, where substantial agreement was seen (119). As with definitions, similar was seen with screening tools - poor to moderate agreement between tools was suggested, as indicated by the variability in estimated prevalence (119). The sensitivity, specificity, positive and negative predictive values of the tools were also compared against each definition, finding that the Ishii Formula had the best sensitivity and negative predictive value, but EWGSOP 2010 was the most specific tool, identifying 88 – 91% of cases of sarcopenia, depending on which definition was used (119). This disagreement is further exacerbated when comparing the original EWGSOP 2020 criteria and EWGSOP2 criteria, with the prevalence of sarcopenia suggested to be significantly lower using the EWGSOP2 criteria, possibly due to the increased sensitivity of this criteria (73, 122).

It is noted that most validation studies for the screening tools are in community-dwelling populations (103, 104, 110, 119, 123), therefore the validity of the tools in detecting sarcopenia in patients with cancer, or hospitalised patients, is unclear. Likewise, although categories for sarcopenia; of acute, chronic, age or disease-related, are potentially useful, methods for screening do not differentiate between these categories, and research into the management of sarcopenia, by category, is in its infancy.

Although the algorithm has been produced (17), its validity has yet to be determined in clinical practice, and the clinical utility of the additional components, which include measures of muscle strength and muscle quality, such as grip strength and bioimpedance analysis, have not been reviewed. Questions regarding the additional time required to complete the algorithm, and the availability of these measures in clinical practice, need addressing to determine the tool's practicality of use.

Finally, the diagnostic criteria for sarcopenia, of low muscle strength, plus low muscle quality or quantity, or low physical performance, overlap with other conditions associated with wasting, such as cachexia; where decreased muscle strength, low fat-free mass (22), and even sarcopenia itself (19), are suggested as diagnostic criteria of cachexia. Similar overlaps exist with diagnostic criteria for malnutrition.

Together, these issues raise the need for investigation into the validity of the SARF-F algorithm in clinical practice, and among hospitalised older adults with cancer, to determine if it is appropriate for use in this setting. Similarly, investigation regarding appropriate thresholds of markers of sarcopenia in predicting patient outcomes is also required. Finally, investigations into the ability to untangle sarcopenia from cachexia, and malnutrition, require thought.

1.4 A comment on frailty

It is important to mention the overlap between sarcopenia and frailty. Frailty has been defined as *"a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability"* (124), or *as "a progressive age-related decline in physiological systems that results in decreased reserves, which confers vulnerability to stressors and increases the risk of adverse health outcomes such as disability or death*" (125). Frailty has many overlapping features with sarcopenia (65), malnutrition (126) and cachexia (127) but has been argued to be a distinct form of multimorbidity and disability (125, 127). However, disentangling frailty from these nutrition-related syndromes, sarcopenia in particular, is challenging:

Like frailty, sarcopenia is also defined by the loss of muscle strength (17), as a condition of ageing (17, 125), is also associated with poor health outcomes (17, 121), and is itself thought to be a major component of frailty (125). This has resulted in the relationship between frailty and sarcopenia being contested, with arguments relating to whether frailty causes sarcopenia, if sarcopenia is a symptom of frailty, or if frailty accelerates sarcopenia (65, 124, 125). Some have suggested that these arguments are fruitless (65), as disentangling the conditions when both are present is almost impossible (65), especially when both lack agreed-upon operational definitions (65). However, at the heart of this, primary sarcopenia can be thought of as specific to muscular-skeletal deficits, causing functional impairments (65, 124), whereas frailty affects many physiological systems, and is specific in its requirement for cumulative deficits, from cardiovascular to immunity (65). However, it is this multi-system dysfunction that results in difficulty disentangling frailty from malnutrition, secondary-sarcopenia, and cachexia, as these conditions are the cause, and or consequence of multi-system dysfunction in older adults with cancer (17, 126, 127).

Multifaceted assessments for frailty itself, such as the comprehensive geriatric assessment (CGA) have been well validated for the identification and management of frailty in cancer patients (128). Because of this, and this thesis' focus on wasting disorders, frailty will not be discussed to the same extent as sarcopenia, cachexia, and malnutrition.

1.5 An introduction to "Mal nutrition"; bad nutrition

As with cachexia and sarcopenia, defining malnutrition has been a stepwise process. There are over 15 malnutrition definitions (62), ranging from focusing on inadequate food intake (129), to inclusion of unbalanced or excessive nutritional intake (130, 131), and impaired assimilation or utilisation (131). Definitions also include effects on growth, function (132), and clinical outcomes (133). The two definitions most commonly used are*; "a state of nutrition in which deficiency or excess (or imbalance) of energy, protein, and other nutrients cause measurable adverse effects on tissue/body function (shape, size and composition) and clinical outcome"* by the British Association for Parenteral and Enteral Nutrition (BAPEN) (134, 135), and *"a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease"* by ESPEN (133, 136). Whist malnutrition can mean under- or over-nutrition, for this thesis, the term malnutrition will be used to refer to undernutrition only.

A third definition of malnutrition, aiming to address its aetiology, and the role of inflammation has also been produced. An international guideline committee, including members of the America Society for Parenteral and Enteral Nutrition (ASPEN) and ESPEN Congress, published consensus diagnostic criteria for malnutrition in adults in a clinical setting (137). This definition divides malnutrition into three categories; i) starvation-related malnutrition; pure chronic starvation without inflammation, ii) chronic disease-related malnutrition; where a chronic disease or condition causes sustained mild to moderate inflammation, and iii) acute disease or injury-related malnutrition; where acute disease or injury causes a marked inflammatory response (137). These divisions, based on the presence, absence, or duration of inflammation, highlight the role and impact of the inflammatory response and catabolism in malnutrition, outlining how nutritional requirements, and therefore malnutrition treatment, is altered by the inflammatory state, and that the pathophysiology of malnutrition varies by the presence or absence of inflammation (137). This definition justly highlights the increase in nutritional requirements, or the required nutritional input, to compensate for increased nutrient utilisation during an inflammatory response. However, the inclusion of an inflammatory response, or disease effect, within the malnutrition definition suggests an inclusion, or overlap of cachexia.

As with cachexia, and sarcopenia, threshold and markers used for malnutrition vary. **Table 7** outlines commonly used malnutrition diagnostic criteria, with their markers and thresholds. Despite endorsement by key nutrition societies, the validity of these criteria is unclear. Evidence for the NICE, 2006 criteria, the guide most commonly used in clinical practice to

diagnose malnutrition, is graded as 'good practice point' [D(GPP)], indicating they were developed from the experience of the guideline development group only, as no appropriate evidence or formal consensus existed to produce evidence-based guides (138).

A pilot study (139) of the ASPEN and AND consensus criteria (140) was unable to determine their validity due to under-recruitment, and highlighted the need for a well-powered study. Validation of the ESPEN consensus statement criteria (140) was conducted with 632 inpatients, with concurrent validity evaluated using the patient-generated subjective global assessment (PG-SGA), a nutritional assessment tool (141). Predictive ability was assessed against patient length of stay (142). The study found that a malnutrition diagnosis was associated with increased length of stay, but the criteria had poor sensitivity, of 17.1% compared to the PG-SGA (142). However, the appropriateness of using the PG-SGA as a validation tool is questionable, as it was initially designed for use with end-stage renal disease patients (143). Also, the rationale for using a nutritional screening tool to validate malnutrition diagnostic criteria is dubious. Another study, investigating the relationship between malnutrition diagnosed with ESPEN criteria and mortality, found no associations at three months (144), however the sample size and short follow-up period appear inappropriate.

A more recent consensus criteria for the diagnosis of malnutrition was posed by the Global Leadership Initiative on Malnutrition (GLIM) published in 2019 (145). These criteria include a two-step process in identifying malnutrition, looking at phenotypic and etiologic criteria for malnutrition (**Table 7**) However, it is noted that definitions and diagnostic criteria for both cachexia and sarcopenia were used in the production of this tool, and the diagnostic scheme for malnutrition posed by GLIM includes markers of both cachexia and sarcopenia (145). Validation studies for the GLIM criteria are emerging, but show variable overlap with other screening methods (146-149).

Table 7: Diagnostic criteria for malnutrition

	Diagnostic Criteria for Malnutrition	**Methodology**
NICE 2006 guidelines (138)	Body mass index <18.5kg/m^2 or Unintentional weight loss >10% 3-6/12 or Body mass index <20kg/m^2 with unintentional weight loss >5% 3-6/12	Recommendation for best practice based on the experience of the guideline development group
ASPEN and AND consensus statement (150) for 'moderate malnutrition'	Two of the following 5 criteria; **Insufficient energy intake:** <75% of estimated energy requirements for >7 days **Weight loss:** 5% in 1 month, or 7.5% in 3 months, 10% in 6 months, 20% in 1 year. **Subcutaneous fat loss:** mild / moderate / severe. **Muscle mass loss:** mild / moderate / severe. **Fluid accumulation:** mild / moderate / severe.	International consensus guideline committee, using characteristics recommended for the diagnosis of adult malnutrition by a working group within ASPEN and AND
ASPEN and AND consensus statement (150) for 'severe malnutrition'	2 of the following 6 criteria; **Insufficient energy intake:** <50% of estimated energy requirements for >7 days. **Weight loss:** >5% in 1 month, or >7.5% in 3 months, >10% in 6 months, >20% in 1 year. **Subcutaneous fat loss:** mild / moderate / severe. **Muscle mass loss:** mild / moderate / severe. **Fluid accumulation:** mild / moderate / severe. **Reduced grip strength:** measurably reduced.	
ESPEN consensus statement (140)	One of the following options; **Option 1:** Body mass index <18.5kg/m^2 **Option 2:** Unintentional weight loss of >5% in 3 months, or >10% unspecified time, plus either Body mass index <20kg/m^2 in those aged <70 years, or <22kg/m^2 in those aged >70 years, OR low fat free muscle index of <15kg/m^2 in women, and <17kg/m^2 in men.	Modified Delphi process involving clinical scientists
GLIM criteria (145)	Use of validated screening tool, plus;	Core representative of; ASPEN, ESPEN,

	One or more of **Phenotypic criteria;** non-volitional weight loss of >5% in 6 months, or >10% beyond 6 months. Low Body mass index of <20kg/m^2 if aged <70 or <22kg/m^2 if >70 years. Reduced muscle mass by validated technique. PLUS One or more of **Etiologic criteria;** Reduced food intake or assimilation of ≤50% of energy requirements for >1 week, or any reduction for >2 weeks, or any gastrointestinal condition that severely impacts food assimilation or absorption. Inflammation from acute or chronic disease burden or inflammatory condition.	FELANPE (Latin American Federation of Nutrition Therapy, Clinical Nutrition and Metabolism), PENSA (The Parenteral and Enteral Nutrition Society of Asia)

1.5.1 Malnutrition in cancer patients

Causes of malnutrition in people with cancer are wide-ranging, and can include tumour-rated factors, effects of anti-cancer therapies and treatments, metabolic inflammatory stress, and social factors (12, 151-153). As malnutrition has many aetiologies, its management in cancer patients varies, and differs based on disease severity and patient preferences and goals. Mechanisms of malnutrition in cancer are summarised in **Table 8**. Each causal factor results in either increased nutritional requirements, or reduced nutritional intake, altering the balance of intake or uptake versus utilisation; resulting in malnutrition.

Table 8: Causes of malnutrition in people with cancer

Mechanism	Consequence	Cause	Nutritional effect
Tumour-related factors	Mechanical obstruction	Gastrointestinal obstruction by tumour, e.g. oesophageal cancer, bowel obstruction	Nausea and vomiting, constipation, pain, ascites, dysphagia, resulting in reduced dietary intake. Obstruction preventing dietary intake (12, 151, 154).
	Functional obstruction	Muscle infiltration or nerve damage by tumour	
	Infiltration	Tumour growth into organs e.g. pancreatic or liver infiltration. Neuroendocrine tumours (NET) affecting gastrointestinal tract.	Organ dependent; pancreatic insufficiency or NET causing malabsorption and steatorrhea, liver infiltration affecting macronutrient synthesis (12, 151).
Anti-cancer Therapies	Chemotherapy	Chemotherapy adverse effects or toxicity	Gastrointestinal effects e.g. nausea, vomiting, diarrhoea, constipation, reflux, mucositis, malabsorption. Fatigue, anorexia (12, 151).
	Radiotherapy	Position dependent radiotherapy	Salivary gland dysfunction, dysphagia, pain, tissue ulceration, taste changes, enteritis (151, 152).
	Surgery	Site dependent e.g. head and neck, gastrointestinal	Xerostomia, dysphagia, pain, reflux, early satiety, anorexia. Gastrointestinal; dumping

			syndrome, pancreatic insufficiency, malabsorption, diarrhoea, constipation, electrolyte losses (151).
Metabolic stress	Metabolic disturbances	Metabolic response associated with chronic illness	Wasting of lean mass, increased catabolism, proteolysis (153).
	Anorexia	Anti-cancer treatment side effects; gastrointestinal symptoms, pro-inflammatory cytokines, psychosocial factors	Reduced dietary intake (23, 151, 152).
	Cachexia	See **Table 1**	Muscle wasting, adipose loss and appetite suppression (36).
Social factors	Psychosocial factors	Social isolation, emotional distress, mobility issues, poverty, depression	Food insecurity, anorexia, dietary restriction, reduced dietary intake (152, 153).

1.5.2 Clinical implications of malnutrition

Many individuals, particularly those with cancer, are at high risk of malnutrition from multiple aetiologies (155). This is reflected in prevalence estimates, of approximately 5% of all adults in England at risk of malnutrition, increasing to 34% of adult hospital inpatients (156), and 25% to 71% of patients with cancer, depending on diagnosis (12, 155). However, it is important to note that for these estimates, 'malnutrition' has been diagnosed in various ways, including a 'medium or high risk' of malnutrition according to the Malnutrition Universal Screening Tool (MUST) (157, 158), 'at risk' according to the Mini Nutritional Assessment (MNA), or a diagnosis based on BMI, weight loss, or objective indexes using biomarkers, such as the Prognostic Nutritional Index (11, 157).

Percentage weight loss is a frequently used malnutrition marker. A review of cancer patients found that 24 – 75% of patients experienced a 5% weight loss over a 6-month period, with the highest prevalence seen in patients with upper gastrointestinal or lung cancers (159). However, these markers of malnutrition vary significantly, as discussed in section **1.5.4**.

As malnutrition affects substantial numbers of people, with older adults, and those with morbidity predominantly affected (156), it is important to understand the consequences of malnutrition, particularly related to older adults with cancer. A meta-analysis found that malnourished cancer patients were at 1.73 times the risk of all-cause mortality, compared to those with an adequate nutritional status (11), with treatment for malnutrition associated with significantly lower hospital mortality rates (160).

Financially, estimations suggest that malnutrition cost the NHS £19.6 billion in 2011-2012, with approximately half spent on older adults (156). Costs include those from increased hospital length of stays and social care requirements (156). Malnourished patients are at a 70% higher risk of falls (161), and are also at higher risk of delayed wound healing and reduced skin integrity due to inadequate reserves, increased inflammation, and a loss of lean body mass (153, 162). Malnutrition is also associated with functional impairment (163), and is an independent determinant of hand-grip strength and functional status in cancer patients (163, 164). With this, there is a question regarding cause and effect; if malnutrition reduces the capacity for activities of daily living, or if a reduced ability to complete activities of daily living, increases malnutrition risk. As with cachexia (40), malnutrition and social isolation are intrinsically linked, with causes of malnutrition, such as eating difficulties or dysphagia (152), and consequences of malnutrition, including reduced functional capacity, reducing patient's ability or desire to socialise (163), interlinked. Malnutrition is also related to increased anti-cancer treatment toxicities, with a review of 16 studies finding malnutrition, assessed using the

MNA tool, was associated with poorer survival in patients receiving chemotherapy, and with early chemotherapy discontinuation (8, 9). Weight loss is also associated with chemotherapy toxicity (8, 165). Additionally, older adults with malnutrition are more likely to experience poorer quality of life, with interventions to improve nutritional status associated with improvements in quality of life (166). This is also seen in adults with cancer, with malnutrition, identified using MNA, being an independent determinant of reduced quality of life in relation to physical function in patients with non-small cell lung cancer (167). Similarly, malnutrition diagnosed using the MNA- Short Form (MNA-SF), was associated with a reduced health-related quality of life in older adults with cancer in a multicentre study (168). This improvement in quality of life with interventions aimed at improving nutritional status is also seen in adults with cancer, such as nutrition support in head and neck cancer patients receiving treatment (169), or use of pancreatic enzyme replacement therapy in pancreatic cancer patients (170).

1.5.3 Management of malnutrition

NICE guidelines recommend malnutrition treatments should take into account patients' needs and preferences, ensuring, as will all medical treatments, patients who are able to make informed decisions regarding their care are given the appropriate information to do so (138). Nutrition support, the provision of nutrition beyond that provided by dietary food intake, is indicated in people who are malnourished, as according to the NICE, 2006 criteria, see **Table 7**, or who are at risk of malnutrition, identified as; no or minimal nutritional intake for > five days, or expected to have no or minimal nutritional intake for ≥ five days, or poor absorptive capacity, high nutrient losses, or increased nutritional needs (138). Nutrition support is recommended for all patients, except those receiving end of life care (138, 171).

The management of malnutrition is not within the scope of this thesis; therefore, a brief summary only has been provided. Methods for nutrition support broadly fit three categories; oral nutrition support, enteral nutrition support, and parenteral nutrition support (138), see **Table 9**.

Table 9: Malnutrition management strategies

Management strategy	Prescribing criteria / indication	Considerations	Additional considerations in oncology
Dietary counselling / food fortification; supplementation of existing diet. Oral nutritional supplements; prescribed products.	ACBS criteria for prescribing oral nutritional supplements; short bowel syndrome, dysphagia, pre-operative preparation of undernourished patients, irritable bowel disease, total gastrectomy, bowel fistulae, or disease-related malnutrition (chronic or acute) (172, 173).	Skills required to modify foods; food preparation, obtaining additional foods. Nutritional adequacy of fortified diet; reliance on calorie and protein supplementation without micronutrients. Time-period of supplementation; 'nutritional completeness', medical conditions, prescriptions expenses, taste fatigue, product over-reliance.	Flavour and texture; taste changes or dysphagia caused by treatment. Ease of use and portability of supplements; frequent / daily hospital visits. Financial cost and 'nutritional completeness' of supplements; potentially sole source of nutrition. Goals of treatment; inappropriate pressure for use, 'medicalisation of food', prevention of preferred dietary intake (12, 171, 172).
Enteral nutrition; provision of nutrition to the gastrointestinal tract via a tube, includes; nasogastric, nasojejunal,	Indicated if defined as malnourished / at risk of malnutrition, with an inadequate or unsafe oral intake, with a functional and accessible gastrointestinal tract. Post-pyloric feeding considered with upper gastrointestinal dysfunction or an	Expected length of time of enteral feeding, dictates type of feeding tube. Patient's wishes, needs, ability to undertake tube care, risks of tube-dislodgement, discharge plans. Gastrostomy / jejunostomy feeding indicated if long-term enteral feeding expected (138).	Common indications include; upper gastrointestinal obstruction, post-operative feeding, dysphagia, severe treatment side effects: causing inadequate nutritional intake and increased nutritional requirements (12). Prophylactic feeding tubes are indicated with cancers of the upper aerodigestive tract (174).

gastrostomy, or Jejunostomy tubes.	inaccessible upper gastrointestinal tract.	Tube placement may cause discomfort, pain, and embarrassment due to visible feeding tube.	Consider overall goals of feeding, particularly in palliative and end of life care; enteral feeding may prolong life, or place burdens on patients and their carers (175).
Parenteral nutrition; provision of intravenous nutrition	Indicated if malnourished or at risk of malnutrition, plus, either; inadequate or unsafe oral and/or enteral nutrition intake, or non-functional, inaccessible, or perforated gastrointestinal tract (138).	Infection risk, burdens on patients / carers, goals of treatment, expected benefits. May improve health-related quality of life and physical function where parenteral nutrition is the only viable option (176).	May be indicated due to bowel obstructions / pseudo-obstructions, post-bowel surgery, severe mucositis preventing absorption, fluid and electrolyte management for high-output stomas.

1.5.4 Identifying malnutrition

To detect malnutrition, many nutritional screening tools have been developed, however, the sheer number produced may have contributed to the problems in identifying malnutrition in practice.

A recent systematic review (18), found 19 separate malnutrition screening tools, where validation studies have been conducted. This excludes shortened versions of tools; such as the MNA-SF, which are produced from, and validated against, the original full-length screening tools (18, 177). In this review, the 3 Minute Nutrition Screening (3-MinNS) tool (178) was identified as the tool which best incorporated the ESPEN consensus definition for malnutrition (140), with high sensitivity and specificity, >80%, against the Subjective Global Assessment (SGA) (141, 178). The 3-MinNS has been validated in two studies; both in hospitalised adult inpatients, against the SGA (178, 179).

However, all tools show inconsistencies regarding their validity; they are often validated against the SGA which itself is not well validated, are validated against other screening tools, or against dietitians' opinions (18). The tool's content also vary with regards to identifying the balance of intake and demand. Only 14 of the 19 tools enquire about dietary intake, six require weight loss quantified over a specified time, and seven enquire about metabolic demand (disease state) (18). Of these, only five ask about both nutritional intake and metabolic demand (18). Similarly, the populations for which these tools were developed vary. Although most, such as MUST (158) or the Nutrition Risk Score (NRS-2002) (180), were developed and validated for use with hospital inpatients, they are often used in outpatient or community settings (180, 181). Finally, as well as varying content, thresholds used as markers of malnutrition vary, for example body mass index, a marker of malnutrition used in 13 full-length screening tools, has thresholds varying between 16kg/m^2 for the Spinal Nutrition Screening Tool (182), 17kg/m^2 for the 3-MinNS (178), to 20kg/m^2 for MUST (158). **Table 10** details the three commonly used malnutrition screening tools, highlighting the variability in content and marker thresholds.

Table 10: Comparison of markers and thresholds used in three commonly used malnutrition screening tools

Category	Screening tool	Marker	Timeframe	Threshold
Body mass index	MUST	Body mass index	NA	>20kg/m^2, 18.5 – 20kg/m^2 and <18.5kg/m^2
	3-MinNS	Body mass index	NA	>20kg/m^2, 18.5 – 20kg/m^2, 17 – 18.5kg/m^2, <17kg/m^2
	NRS-2002	Body mass index	NA	< / ≥ 20kg/m^2
Weight loss	MUST	Unplanned weight loss	3 – 6 months	<5%, 5 – 10%, >10%;
	3-MinNS	Unintentional weight loss	No timeframe specified	No, 1 – 3kg, 3 – 7kg, >7kg
	NRS-2002	Weight loss in last 3 month	3 months	Yes / No
Dietary intake	MUST	Acute illness and reduced intake	> 5 days	Has been or likely to be no nutritional intake
	3-MinNS	Nutritional intake	1 week	Tube feed; >1.5 l/day, <1.25 – 1.5l/day, 1 – 1.25l/day, <1/day Diet; ¾ - 1 portion/meal, ½ - ¾ portion/meal, ¼ - ½ portion / meal, starvation or <¼ portion/meal
	NRS-2002	Reduced dietary intake	1 week	Yes / No
Disease state	3-MinNS	Disease with nutrition risk	NA	None, dialysis, cancer/infection/pressure sore/post major surgery
	NRS-2002	Severely ill	NA	Yes / No
Muscle loss	3-MinNS	Muscle wastage	NA	Temple; well defined, slight depression, hollowing Clavicle; no protrusion, slight protrusion, prominent protrusion

(158, 178, 180)

Key: MUST = Malnutrition Universal Screening Tool, 3-MinNS = 3 Minute Nutrition Screening tool, NRS-2002 = Nutrition Risk Screening

1.5.5 Gaps in the evidence

As with cachexia and sarcopenia, definitions and diagnostic criteria for malnutrition have been produced by consensus, and lack high levels of evidence confirming their appropriateness for use; there is little work regarding the validity of the diagnostic criteria, particularly in relation to their predictive ability. However, without a consensus definition, selecting appropriate diagnostic criteria is challenging. This is particularly emphasised with the inclusion of inflammation, and disease burden, as defining aspects of malnutrition (137, 183), **Figure 2**. However, this goes against the recognition that, in some cases, malnutrition is caused by starvation only. As previously suggested (see **Table 7**), including inflammation in malnutrition's diagnostic criteria contributes to the overlap between malnutrition and cachexia; with inflammation being a key cachexia symptom (36, 43), but also an aetiology of malnutrition, with inflammation increasing nutritional demands.

The international guideline committee suggests a need for several malnutrition diagnoses due to differing aetiologies (137), which possibly suggests that different medical conditions require different malnutrition diagnostic criteria. Although understandable, this further complicates the interplay between malnutrition and cachexia, with a question of if malnutrition is caused by a disease, or an inflammatory response, when does malnutrition become cachexia?

However, rather than a focus on inflammation or disease state, a focus on the balance between intake and demand, could be argued as key. When diagnosing malnutrition the physiological consequences, such as weight loss, low BMI or functional decline, in their simplest form, are caused by inadequate nutrient intake or uptake, or increased nutrient utilisation or demand (150), with inflammation also increasing nutrient demand. This suggests a possible emphasis on these is required when diagnosing malnutrition.

Another issue is the variability in the content of malnutrition screening tools, see section **1.5.4**, of both markers of malnutrition, and their thresholds. With a lack of consensus regarding definitions or diagnostic criteria, and evidence of their validity, it is unclear which markers, and at what threshold, are most appropriate to identify malnutrition. This is compounded by overlapping makers of malnutrition with both cachexia and sarcopenia.

This overlap is particularly obvious when looking at the requirement for lean and fat mass loss as defining characteristics of all three conditions (17, 19, 22, 135, 136). In clinical practice, overall or percentage weight loss, and current body mass index, are often the sole anthropometric measures recorded, rather than specific measures of lean body mass. It is not possible to determine the aetiology, or contributing factors of this weight loss, from these measures alone. This is particularly so in older populations, populations with advanced

diseases, or multimorbidity, where prevalence estimates of malnutrition, sarcopenia and cachexia are higher (12, 13).

An additional query is in regards to the appropriateness of malnutrition screening. NICE 2012 guidelines (14) recommend that people in care settings, including hospitals and primary care, are screened for malnutrition risk using a validated screening tool. Screening tools are considered valid if studies have assessed that a tool measures what it intends to measure, and has measures that are reproducible and acceptable to use (14). However, as highlighted, malnutrition prevalence estimates vary by the tool used (15). A key example is provided when comparing three common screening tools against the ESPEN consensus criteria in patients with gastrointestinal cancer, the prevalence of malnutrition was; 20% according to ESPEN criteria, 37.6% with MUST, 47.8% with the MNA-SF, and 52.2% according to the NRS-2002 tool (15). This questions the validity of malnutrition screening tools, particularly in complex populations where other clinical conditions, such as cachexia, may modulate the results.

Another issue relates to the wider effects of nutritional screening. When considering who to screen, and what nutritional interventions are appropriate, benefits and burdens must be considered. Routine nutritional screening is considered inappropriate for patients receiving end of life care (171). Instead, a focus on comfort and enjoyment of diet, rather than managing malnutrition is promoted, alongside counselling to address patient, family, or carers concerns regarding dietary intake (171). This also raises questions regarding if patients wish to be screened for malnutrition? Interestingly, NICE guidelines highlight that there is no clear evidence whether nutritional screening programmes are beneficial, or what is the most appropriate way to carry out screening (138). This is compounded by the fact that studies assessing the efficacy of nutritional interventions have been of poor quality or at high risk of bias (184), and have not shown nutritional support to affect long-term mortality rates (184).

Although the impact on clinical staff's time, an estimated 6–12 minutes per patient screened (171), has been investigated, little consideration of the impact of nutritional screening on patients has been made. Screening for medical conditions, for early detection or prevention, is conducted routinely, however balancing potential benefits against potential burdens is important when deciding who to screen and how often (185). For example, when discussing cancer screening, the harms of a false-positive, iatrogenic complications, or anxiety whilst awaiting results are more appreciable (185). However, the impact of nutritional screening, a generally non-invasive and routine screening method, has rarely been assessed. From this, questions regarding patients' opinions and experiences of nutritional screening must be asked. This is particularly pertinent for older adults with cancer, where the perceived likelihood of,

and risk from malnutrition is higher, and patients are more likely to be routinely screened and offered nutritional interventions.

As mentioned throughout, the overlap between malnutrition, sarcopenia, and cachexia, presents a challenge when trying to identify and managing these conditions. As shown in sections **1.2.2**, **1.3.4**, and **1.5.3**, the treatments of these conditions vary, with a focus on physical rehabilitation for sarcopenia, medical management of cachexia and dietary interventions for malnutrition (52, 102, 138). To ensure the most appropriate treatment for each is provided, the ability to distinguish one condition from another, and to identify the relative contribution where more than one is present, is paramount.

Suggestions for a screening tool that can discriminate one condition from another have been made. Most recently, Miller et al., 2018, suggested the inclusion of the following components in a new screening tool; quantification of weight loss, body mass index, assessment of dietary intake and appetite, underlying health state, consideration of age, assessment of muscle mass and function, and assessment of metabolic derangements and inflammation (18).

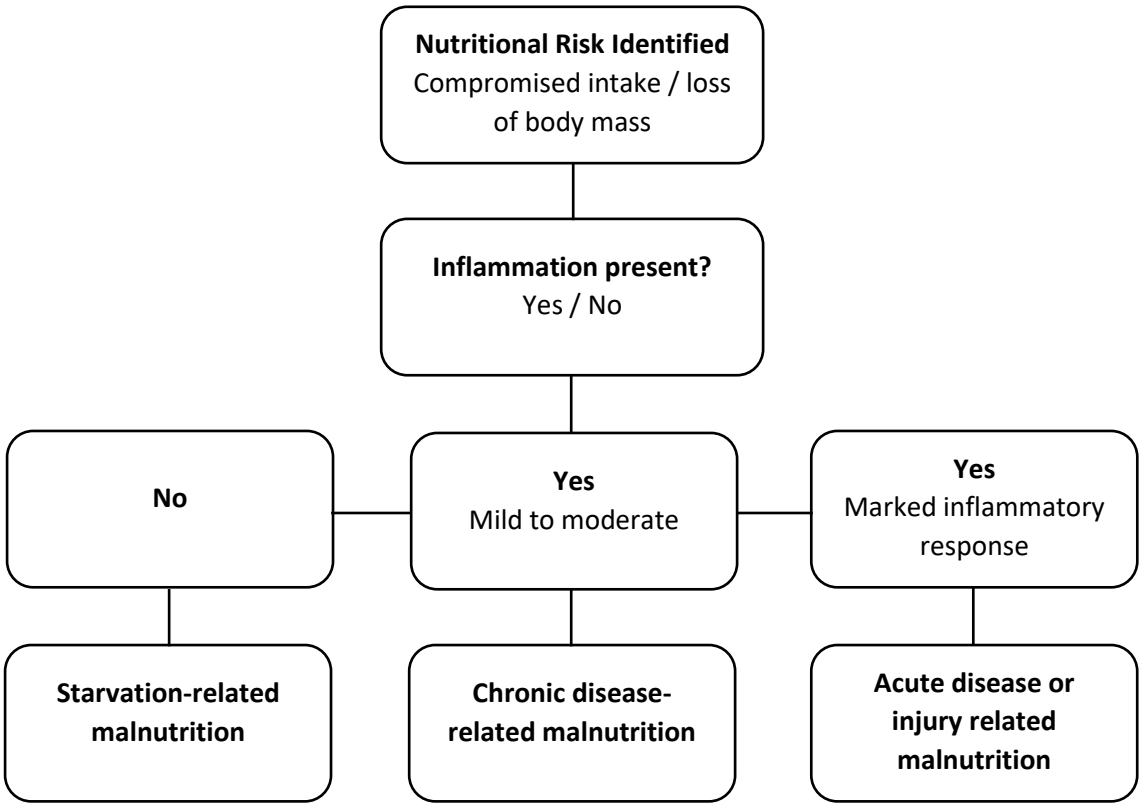


Figure 2: Aetiology-based malnutrition definitions

Adapted from Jensen et al., 2009 and White et al., 2012; figure: Aetiology-based Malnutrition definitions (150, 183).

1.6 Questions requiring consideration

This introduction presents several questions in relation to malnutrition, sarcopenia, and cachexia in older adults with cancer. These can be summarised as;

- What is the overlap between malnutrition, sarcopenia and cachexia, particularly in older adults with cancer, who are at a higher risk of developing each of the conditions due to factors including age and diseases status? (12, 27, 90);
- Although screening tools for malnutrition, sarcopenia, and cachexia have been produced, their clinical utility, particularly in relation to screening for sarcopenia and cachexia, has not been established. Are these tools clinically useful in older adults with cancer? (16, 17);
- There is variability in prevalence estimates of malnutrition, depending on the screening tool used, questions the validity of the screening tools (12, 13). Similarly, markers and marker thresholds used in screening vary greatly. What are the most appropriate variables and thresholds to use to detect malnutrition in older adults with cancer?;
- Although nutritional screening is recommended for all patients, except for those receiving end of life care, the benefits, and subsequent burdens of screening have not been well established. Is there a legitimate need for nutritional screening in older adult with cancer? (14, 185);
- Should we screen for cachexia and sarcopenia? Considering the issues with malnutrition screening, the potential overlap with, and therefore possible incorrect treatment of malnutrition, sarcopenia, or cachexia, and current unknown appropriate treatments for cachexia (52), is screening appropriate?
- Similarly, do patients wish to be screened for malnutrition, sarcopenia, and cachexia?;
- With the overlap of malnutrition, sarcopenia, and cachexia, are the estimated prevalence of the conditions accurate? As estimates of the prevalence for cachexia rely on reported weight loss, this may inaccurately encompass malnutrition or sarcopenia (8);
- Previous studies suggest components for a combined screening tool for malnutrition, sarcopenia, and cachexia (18), are these suitable and applicable in a clinical setting?

1.7 Summary

This chapter summarises the current definitions and diagnostic criteria, for malnutrition, sarcopenia, and cachexia, as well as the clinical implications of these conditions, and methods for their identification.

In summary, malnutrition, sarcopenia and cachexia are three complex conditions; in relation to their detection in clinical practice, and their effect upon patient's wellbeing, of the impact on the efficacy of anticancer treatments, and upon older adults with cancer survival. The challenges associated with these conditions are complicated by the similarities between the three; of their overlapping clinical diagnostic criteria, particularly the inclusion of weight loss, and loss of muscle mass as a criterion for each condition, which makes detecting and distinguishing between each condition problematic. This raises the need for a way to identify, assess and differentiate between the three conditions, particularly in the population of older adults with cancer, who are at an increased risk of malnutrition, sarcopenia, and cachexia, due to their diagnoses and age.

The next chapter outlines the aims and objectives of this thesis, and how this thesis will address the issues raised in this introduction.

Chapter 2: Research questions

2.1 Introduction

In **chapter one**, the gaps, discrepancies, and issues with the current literature regarding malnutrition, sarcopenia, and cachexia in older adults with cancer were discussed, which included:

- The unknown overlap between malnutrition, sarcopenia, and cachexia, particularly in older adults with cancer, who are at high risk of developing each of the three conditions;
- The variability of malnutrition prevalence estimates depending on the nutritional screening tool used, questioning both the validity of the tools, and the thresholds used for the markers of malnutrition;
- The clinical utility of screening tools for malnutrition, sarcopenia, and cachexia;
- The benefits and burdens of nutritional screening, and screening for sarcopenia and cachexia in clinical practice, particularly in light of the overlap between the three conditions;
- Patient opinions of nutritional screening, and of screening for sarcopenia and cachexia;
- The feasibility of screening for malnutrition, sarcopenia, and cachexia simultaneously in clinical practice.

This chapter will develop distinct research questions aimed at addressing these gaps.

2.2 Impact of COVID-19 pandemic

Due to the impact of the COVID-19 pandemic on a number of aspects of this thesis, the thesis aims and objectives, to address the research questions identified in chapter one, were modified midway through the thesis. This primarily affected the focus of the mixed-methods study, as discussed below. This chapter will outline the amended thesis aims and objectives, with the original thesis aims and objectives outlined in **Appendix 1**, which highlights the changes to the research aim, objectives and research questions made to compensate for the challenges presented by the pandemic.

2.3 Overarching research aim

The overarching aim of this thesis was to:

- To understand better the prevalence, detection, assessment, and patients' experiences of malnutrition, sarcopenia, and cachexia in older adults with cancer

The research questions, objectives, and a summary of the methods used to address this aim are outlined below.

2.4 Research questions

Specific research questions identified from chapter one were:

1. What is the relationship between markers of malnutrition and clinical outcomes in older adults with cancer, in the published literature?
2. What are patients, their families, and carers' experiences and views of nutritional screening, as identified in the published literature?
3. What is the prevalence and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer?
4. What are the experiences and views of older adults with cancer regarding screening for malnutrition, sarcopenia, and cachexia?

2.5 Research objectives

The research objectives, in response to each of these questions, are:

1. To identify, synthesise, and critically appraise the published evidence regarding commonly used markers of nutritional status and clinical outcomes in older adults with cancer.
2. To identify, synthesise, and critically appraise the published evidence regarding patients, their families and carers' views and experiences of nutritional risk screening.
3. To gain exploratory estimates of the prevalence of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer.
4. To explore the interrelationships and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer.
5. To investigate the feasibility of conducting a subsequent adequately powered study to develop, refine, and test, a single, clinically relevant screening tool, able to identify and distinguish between elements of malnutrition, sarcopenia, and cachexia in older adults with cancer.
6. To explore and understand patients' experiences and views of the clinical assessment and management of malnutrition, sarcopenia, and cachexia.

2.5.1 Mixed-methods study questions

Specific research questions posed for the mixed-methods study include:

RQ1: Is it feasible to recruit, and screen a group of older adults with cancer for malnutrition, sarcopenia and cachexia?

RQ2: What are the demographics and clinical characteristics of this group of older adults with cancer?

RQ3: What is the prevalence and overlap between malnutrition, sarcopenia, and cachexia, in this group of older adults with cancer?

RQ4: What is the association between malnutrition, sarcopenia, and cachexia, and key clinical characteristics, in this group of older adults with cancer?

RQ5: What are patients' views and experiences regarding assessments for malnutrition, sarcopenia, and cachexia?

RQ6: What are patients' views of the role of, and understanding of, malnutrition, sarcopenia, and cachexia in cancer?

2.6 Summary of thesis methods

2.6.1 Systematic reviews

To address objective one, a systematic review and critical appraisal of the published evidence regarding markers and measures of nutritional status in older adults with cancer was conducted, and is reported in **Chapter Four**. This review evaluated the evidence regarding markers of malnutrition used in validated screening tools, and objective indexes, to determine if they are appropriate to use to predict outcomes in older adults with cancer.

For objective two, a further review, to synthesise systematically the current evidence regarding patients, their families, and carers' experiences and views of nutritional risk screening was completed, and is reported in **Chapter Five**. This review aimed to evaluate both quantitative and qualitative responses regarding patients' experiences of nutritional screening, to identify the acceptability of screening, alongside barriers to its utility in clinical practice.

2.7 Mixed-methods study

To address objectives three to six, mixed-methods, single centre study, with a convergent parallel design was conducted; in which both qualitative and quantitative research was undertaken separately and simultaneously, with integration of the findings presented. The quantitative and qualitative aspects are reported in **Chapter Seven** and **Chapter Eight** respectively, with the synthesis reported in **Chapter Nine**.

This mixed-methods study comprised of an exploratory observational study, involving screening older adults with cancer, aged ≥70 years, for sarcopenia, cachexia and markers of malnutrition, and subsequent recording of clinical outcomes. Participants were also invited to participate in qualitative interviews regarding their views and experiences of screening. Results were used to inform upon the content of a single screening tool to detect and differentiate between malnutrition, sarcopenia, and cachexia.

An additional stage, to explore patients' and clinicians' opinion of the acceptability and feasibility of a single tool in clinical practice, and refinement of a single screening tool, was planned, however, due to study delays and difficulties with recruitment caused by the COVID-19 pandemic, this stage was not undertaken.

2.8 Summary

In this chapter, the aims, objectives, and research questions addressed by this thesis have been outlined. Next, the thesis' Methodology **Chapter Three** will be described and justified.

Following this, a systematic review of markers of malnutrition (**Chapter Four**); a systematic review of patient experiences of nutritional (**Chapter Five**); the Methods for the mixed-methods study (**Chapter Six**), and results of the mixed-methods observational study with concurrent qualitative interviews (**Chapter Seven** and **Chapter Eight**), will be presented, with a synthesis of the mixed-methods results (**Chapter Nine**), and conclusion and synopsis of the work also presented (**Chapter Ten**).

Chapter 3: Methodology

In this chapter, I shall discuss the methodology that has been used within this thesis. For this, the research paradigm and methodological approaches used, and their application to the thesis will be delineated. At each stage, the options, rationale, and justification for the methodology used, and decisions made, will be discussed.

3.1 Research paradigms

When designing this thesis, considerations of the research paradigm, the 'set of common beliefs and agreements… about how problems should be understood and addressed' (186), must be made. Research paradigms are characterised through their ontology, epistemology, and methodology (187). Ontology can be defined as the study of 'being', of what the world is, and what can be known (188-190). Whereas epistemology is concerned with the nature, or kind, of knowledge itself, and how it is possible to learn about the world (188-190).

Quantitative research often follows a deductive approach; where research is generated from theory (191), resulting in a hypothesis to test, with an objective ontological stance, and a positivist or pragmatic epistemological orientation (191). Whereas qualitative research is more often inductive; with theory developed from the research (191), and often follows an interpretivist epistemological, and constructionist ontology (191), see **Table 11**.

There have been previous arguments that, due to the differences in research paradigms between qualitative and quantitative research, the two methods could be considered incompatible (191), and any integration would only be superficial. This argument relates to the notion that research is defined by its paradigm, and the components used within it, which include the methods, methodology, values and assumptions applied (191). However, this assumption does not consider the strengths of each type of research and its associated paradigms. It also assumes that 'quantitative' and 'qualitative' research have their own specific paradigms, which cannot overlap; an argument that does not hold, as quantitative and qualitative research have many commonalities, and at their core they both aim to examine what people do, and why (191, 192). Similarly, although the approaches may have differing ontological and epistemological stances, these paradigms are not deterministic; their use does not define their results (191).

More recently, the benefits of mixed-methods research, particularly when investigating complex health-related research (192), have been repeatedly justified. Mixed-methods research allows for integration of findings throughout the research process, enabling triangulation of data, and a richer understanding (192, 193), providing a more complete story

than could be achieved from either approach alone (191, 192). Section **3.3** discusses the use of mixed-methods research in this thesis. This methodology also reflects well the practices undertaken by clinicians when assessing and treating patients; the combination of quantitative test results with the patient's own narrative; enabling formation of a complete picture of the patient and their concerns, allowing a holistic approach to their care; placing the patient in the centre of the conversation, and tailoring treatment based on multiple factors, of the patients' experiences and opinions, as well as the quantitative test results. As this thesis aims to address a multifaceted question, a multi-pronged approach – which incorporates quantitative clinical results, and qualitative understanding of patient experiences, is required.

The intertwined methodologies of qualitative and quantitative research for this thesis are illustrated in **Figure 3**.

Table 11: Summary of paradigms

Positivist	*Only observable evidence, or facts, result in legitimate knowledge* **(191)**
Pragmatic	*Use of the most appropriate methodology for the research problem being investigated (194)*
Interpretivist	*Knowledge is socially constructed, and is multiple, and relative* (191)
Constructionist	*knowledge is constructed based on individual's social interaction* (191)

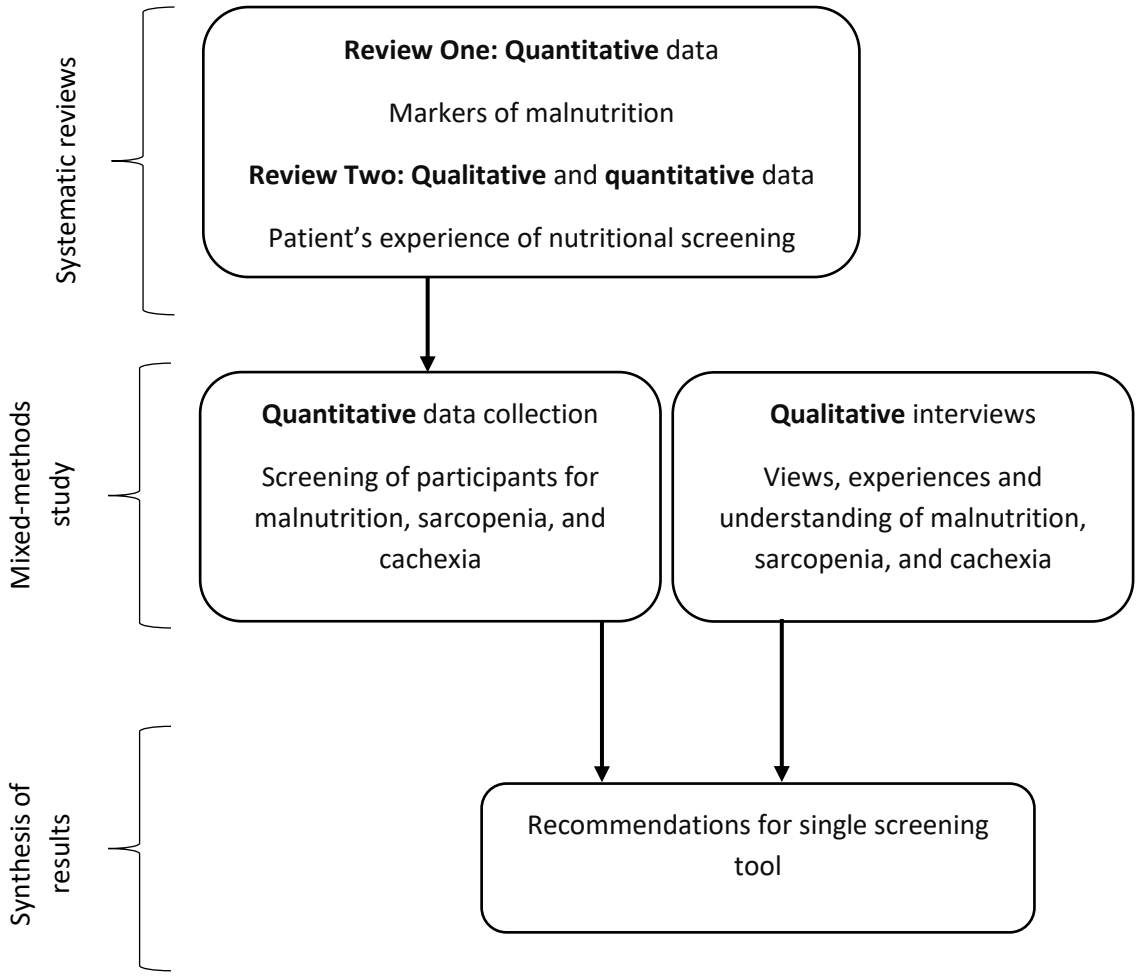


Figure 3: Diagram detailing the planned thesis outline, including the three-stage, mixed-methods observational cohort study with a convergent parallel design

3.1.1 Application to thesis

The overarching purpose of this work was to inform upon a clinical tool that is usable in daily busy clinical practice. Therefore, a pragmatic approach for the research was used. A pragmatic approach enables the production of 'useful knowledge' grounded in reality (195), which is vital when focusing on clinical utility, and research that informs clinical practice.

As the research questions posed required both quantitative and qualitative study designs to produce appropriate answers, a mixed-methods approach was employed (see section **3.3**). This required the management of potentially conflicting ontological and epistemological stances. To manage this, a pragmatic research approach; with the aim of using the strength of each form of research, without becoming weighed down by historic research tendencies (191, 193), was used. To ensure a pragmatic approach was employed, appropriate phrasing of the research questions, to ensure the questions themselves determine the research methods, and stance, was necessary (193, 196).

A pragmatic approach allowed a balance of both positivist and interpretivist paradigms; of both generating and testing hypotheses; by both gaining 'rich' data, with depth, from qualitative work, and 'hard' data from quantitative methods (197). For these research questions, neither a solely qualitative or quantitative methodology would have satisfied; a positivist approach would not have garnered data on patient experience, nor would have answered questions regarding clinical utility, whereas a critical or creative approach would not have provided the numerical or statistical data required to inform upon a single screening tool. Without the blended methodology provided through the use of a pragmatic approach, these research questions could not be answered in a clinically useful or constructive way (197, 198).

3.2 Clinical utility

A key objective of this research was to inform upon a tool that is clinically useable and useful. The focus on this comes from my previous experience working as a health care professional in a clinical environment, and seeing the barriers present that impact upon health care professional's ability to provide appropriate, high quality treatment. Reasons can include lack of time, lack of equipment or requirement for specialist tools, costly equipment, inappropriate measures for patient populations, or tools which do not address or detect items which suggest clinical concern. Although screening tools and interventions often have their validity assessed, their 'utility'; ability to provide benefit, and their usefulness in aiding patient care, alongside the ability to use a tool in a clinical environment, is often not assessed.

For example, the validity of the SARC-F, a screening tool for sarcopenia (109), its ability to predict clinical outcomes, and its sensitivity and specificity (112, 199, 200), has been assessed. Although these assessments help answer the question of its validity, of; yes it does detect sarcopenia, it does not answer questions regarding clinicians' or patients' experiences of the tool, or the value that the tool adds to a clinical assessment (201). The feasibility of conducting screening in clinical practice; particularly when screening requires multiple measures of muscle strength, quality, quantity, and physical performance (17), must also be assessed to also help determine the tools clinical utility. The use of a screening tool in a research setting may be very different than in a clinical setting. At present, the feasibility of the SARC-F algorithm, cachexia screening tools, and many of the malnutrition screening tools, have not been assessed (16, 17, 55). It is addressing this lack of information, which has become central to this thesis.

3.2.1 Older adults with cancer

The research in this thesis is focused on older adults with cancer, defined for this thesis as those **aged 70 or over**. For the mixed-methods study, older adults with a multi-disciplinary team (MDT) confirmed diagnosis of certain cancers will be focused on; specifically, patients with **lung** (both non-small cell and small cell), **breast, prostate, colorectal, head and neck or upper gastrointestinal** (including oesophageal, stomach, and pancreatic) cancer.

The reason for the focus on adults aged 70 or over is two-fold; primarily, half of all new cancer diagnoses are in those aged 70 or over (202), with forecasted increases in the number of older adults in the UK, health services must adapt to managing the complex care needs of this ageing population (203). Secondly, sarcopenia is a condition of ageing (17) and malnutrition is more prevalent in older adults (204), and in those with cancer (12). Therefore, older adults with cancer, who are also at risk of cachexia (13), are at increased risk of all three conditions.

The reason for the choice of the six cancer sites include; over half of all new cancer diagnoses in the UK are either breast, prostate, lung, or colorectal cancer (202). Due to the physical site of the cancer, and the impacts of targeted anti-cancer treatments, head and neck, and upper gastrointestinal cancers often impact an individual's nutritional status (202, 205). Similarly, cachexia is thought to be most prevalent in patients with upper gastrointestinal, lung and head and neck cancer (206). Although less common in patients with breast, prostate, and colorectal cancers, estimates for cachexia incidence for these diagnoses still ranges between 11 and 39% (206). These combined suggest that these six cancer sites should provide appropriate prevalence of the three conditions, and appropriate heterogeneity in sample characteristics to produce a clinically applicable screening tool.

3.3 Mixed-methods approach

Mixed-methods research can be summarised as; the employment and embedding of more than one type of research method within a study (193). Mixed-methods research involves the use of multiple types of data, potentially with different investigators, possibly with different research paradigms (193). With this, mixed-methods research can be thought of as 'multi-strategy research', aiming to address complex research questions and designs (191, 193).

It is suggested that mixed-methods research can lead to higher quality research (193). However, using mixed-methods research must be justified, rather than employed due to the increasing popularity and interest in the method (193). For this, the feasibility, and expected benefits of a mixed-methods approach must be considered. Initially, the ability to access and collect both qualitative and quantitative data congruently, and if mixed-method research is appropriate within the research population or topic (193, 207), must be considered. It is often the research population, as well as the research aim, that informs upon the suitability of using a mixed-methods approach (193).

Secondly, the contribution of each research technique – how data produced from each supports the other, and the methodology for data management and integration – must be considered and well designed, to prevent the inclusion of the second research method from becoming tokenistic (193, 207).

A mixed-methods approach allows championing of the strongest aspects of qualitative and quantitative research, combining them to produce rich, in-depth and contextualised data (193, 207). With this, mixed-methods research, if conducted successfully, provides broader views and understanding of results gained (191, 193). Qualitative data can offer explanations of, and provide validity to, nuances in quantitative data (193, 207). Conversely, quantitative data can provide grounding and context to qualitative findings (193, 207). This can be used to generate new perspectives and enrich research (208). It is this ability, to gain boarder views and a more in-depth and detailed understanding, which has made the use of both quantitative and qualitative methods key for answering this thesis' research aim.

3.3.1 Application to thesis

To address the aim of this thesis, a mixed-methods approach; combining quantitative data collection, in the form of an exploratory observational study, supported by qualitative interviews, both informed upon by the results of a systematic review, is pragmatic, and aims to produce a comprehensive answer to the research question. Due to the complexities of nutrition in older adults with cancer (163), the intertwined relationships between malnutrition, sarcopenia, and cachexia (18, 25, 137, 183), the social, as well as clinical factors, which impact

upon these conditions (52, 80, 152), and the importance of older adults with cancer's views and experiences of screening, only a mixed-methods approach, seemed adequate to address these multifaceted issues.

For my research, triangulation of information will be important in answering the research questions. The term triangulation, from the navigational sense of using different bearings to find a central point, can be considered misleading when discussing triangulation in terms of mixed-methods research. As well as corroboration of findings, the term triangulation in mixed-methods research can be used to include;

- Elaboration or expansion, where one data type adds to the understanding of another;
- Initiation, where the use of one method stimulates a new theory or question that can be studied using an alternate method;
- Complementary, where quantitative and qualitative results are analysed separately, then compared to determine if and how they complement each other, and finally;
- Contradictory, where qualitative and quantitative results conflict, where data can be used as evidence to discount one or methods result for another (193, 207).

In this work, elaboration, complementary and contradictory triangulation will be used to answer the research question. Predominantly, complementary triangulation (193) will be used to inform upon the production of a single screening tool, using data on clinical outcomes, and participants' views and experiences of screening. Alongside this, elaboration, of using qualitative methods to help explain quantitative results (193), will also be employed when informing on the single screening tool, particularly if there is a conflict between quantitative data and participant opinions, such as which measures are appropriate to use in the single tool. For this, contradictory triangulation will become important in justifying the addition or removal of variables (193, 207).

3.3.2 Convergent parallel study design

For my study, a convergent parallel study design was chosen. This entails parallel collection of both quantitative and qualitative data, which converge during data analysis to inform upon an initial single screening tool for the three conditions; malnutrition, sarcopenia and cachexia. Additional stages to the mixed-method study were planned, which included initial face and content validity testing, using feedback received from further participant and clinician interviews to refine the single screening tool. However, due to the delays caused by the COVID-19 pandemic, this aspect of the study was not conducted. See **Appendix 2** for the original study protocol.

Equal weight was to be placed on both qualitative and quantitative research for several reasons, including; timescales, possible sample sizes for the quantitative and qualitative aspects of the study, and the benefits of each methodology. As discussed in the study limitations, section **3.6**, due to the scope possible within a PhD, and limitations on possible resources for data collection, an estimated sample size, of 90 to 120 participants, based on recruitment of three to four participants per week was chosen, detailed further in section **6.3.3**. Expected recruitment rates were based upon the expected available number of eligible participants, expected time to collate study measures – which can be time-consuming due to the large number of measures (16, 17), as below, and time to complete qualitative interviews. Additionally, conducting a large-scale quantitative study and gaining an appropriate sample size for a large observational cohort study, was not possible during a 12-month data collection timeline. Due to this expected smaller sample size, triangulation of results, using qualitative data, is particularly advantageous for expanding and explaining the results gained in the observational study.

A convergent parallel design, using both the results from the quantitative and qualitative study aspects, was used to ensure a focus on 'clinical utility' was kept throughout the study. As demonstrated in **Chapter One**, numerous screening tools for malnutrition, sarcopenia, and cachexia have been produced (18). However, the usability of these tools in clinical practice, particularly for cachexia and sarcopenia, had not been assessed. Each tool required several anthropometric measures, blood tests, and questionnaires (16, 17), which can be time-consuming to complete, or unachievable due to a lack of equipment or skills. Additionally, in the population being studied, there is an increased risk of frailty, and the ability of older adults with cancer to complete the measures must be considered. Therefore, gaining qualitative feedback regarding views and experiences of screening is justifiably as important as the quantitative data gained from the observational study.

3.4 Quantitative methods

Quantitative methods were employed as part of this mixed-methods study. What we now think of as quantitative health research dates back as far as the 1750's, when controlled experiments to determine the cause and treatment of scurvy were first conducted by James Lind (209). Lind prescribed daily treatments of either 1.1 litres of cider, dilute sulphuric acid, half a pint of seawater or two oranges and a lemon to 12 sailors, with observations made of their recovery from scurvy (209). James Lind was similarly pioneering with reviews, with a book published in 1753, providing an early example systematic review on the causes of scurvy (209, 210). Fortunately, advancements in health research mean experiments involving seawater and sulphuric acid consumption have dwindled, and more rigorous methods for quantitative research have emerged. Several quantitative methodologies were used in this thesis. Two systematic reviews of the literature, including meta-analyses and data synthesis, as discussed in section **3.4.2,** and an observational study, see section **3.4.7**, were conducted.

The following sections discuss the methodology used for the systematic reviews and observational study, including discussions of key decisions, delimitations, and choices made when designing and implementing the reviews and study.

3.4.1 Types of literature review

For this thesis, an overall summary of the existing research was required to identify the gaps in the current knowledge, and to produce a springboard from which to propel the research in this area. Several options for the format of a review were considered: A recent review (211), exploring all types of published reviews, identified 48 distinct types, including; critical, narrative, scoping, umbrella, rapid and realist reviews. For the topics covered in this thesis, a non-systematic literature review, or narrative review of the literature, could have been conducted. Narrative reviews involve the discussion of key topics and theoretical points of view, and instead of focusing on a specific question, cover a wider topic base, without an explicit focus (212, 213). Narrative reviews often include grey literature, and take a less formal approach (213). However, due to this less formal method, there is an increased risk of bias, introduced from the non-systematic search, and bias introduced from the authors' interpretation of the literature (212, 213). This method was not chosen as there was a need to conduct a rigorous review of the literature and assess and manage the bias within the articles.

A scoping review, which maps the existing literature in an area, involving a systematic search (211), could also have been conducted. The benefit of a scoping review is its ability to present an overview of a body of literature, particularly when an area of literature has not been extensively reviewed or is heterogeneous in nature (214). Scoping reviews are often used as a

preliminary step to a systematic review, to identify areas that require a more detailed review (214). Although the topics covered in this thesis' reviews have not been extensively studied, and scoping reviews involve a systematic search, the synthesis of results provided by a systematic review, including meta-analysis of results, or thematic analysis of results, are more appropriate to answer this thesis' research questions. Similarly, systematic reviews are considered the most valid form of review, particularly for medical evidence (212). Systematic literature reviews, involving a methodical and rigorous approach to comprehensively reviewing the literature, were therefore used.

3.4.2 Systematic reviews

Systematic reviews, a variety of literature reviews, methodologically address a specific research question by collating, appraising, and summarising the evidence base, with the aim of finding the 'true' answer to a research question (215). Systematic reviews specifically address the risks of bias in the literature, with the aim of producing a point estimate of the true research answer (215) and involve the analysis of published evidence, identified from an exhaustive review, against a specific and focused question (213, 216). This is required as all research is at risk of bias, potentially leading to spurious or conflicting results in the literature (215). A systematic review aims to address these biases by evaluating the quality of the available evidence and producing an impartial answer to the research question (215, 217, 218). **Table 12** outlines the types of bias commonly seen, and the management strategies employed to mitigate these biases within a systematic review.

3.4.2.1 Advantages of systematic reviews

Systematic reviews are considered to be a rigorous technique for summarising and mapping the evidence base in an unbiased, methodical, and transparent manner (217, 219). The aim of systematic reviews are to assess evidence quality, and synthesise evidence into an accessible format, which can be used to inform healthcare decisions (217, 219). A key advantage of systematic reviews is their ability to address research biases by accounting for research quality, publication bias, and by evaluating evidence validity (217). Systematic reviews also enable the combination of data from independent studies, which assess the same variables and outcomes, to produce a single point estimate of effect, through the use of meta-analyses (219), see section **3.4.5.1**.

3.4.2.2 Disadvantages of systematic reviews

Despite systematic reviews following an established protocol, several biases can enter the process, reducing the efficacy and reliability of results (212). One method of avoiding reporting bias is through peer-review of systematic review protocols, through submission to the international Prospective Register of Systematic Reviews (PROSPERO) (220, 221). Another

challenge can be ensuring the review is comprehensive; with inherent biases addressed in the planning stages (212). See **Table 12**. Main biases can include; unequal access to journal articles, often due to paywalls, or exclusion of non-English language publications (215, 217), resulting in prejudiced and unreliable results. For the systematic reviews produced as part of this thesis, submission to PROSPERO, use of all-language papers, extensive searching of multiple databases, no temporal limitations, payment for required full-text papers, quality assessments of papers, and publishing in peer-reviewed journals, were all employed as methods used to mitigate biases.

Table 12: Biases addressed within a systematic review

Type of bias	**Definition**	**Mitigating strategy within a systematic review**
Selection bias	Inclusion or exclusion of participants, results, groups, or studies resulting in an alter representation of the sample	Clear reporting and adhesion to review inclusion and exclusion criteria. Double screening of potential studies by independent researchers
Publication bias	Overrepresentation of studies with positive results in the literature, negative results more likely to be rejected for publication	Assessment of publication bias, e.g., with funnel plot, to assess heterogeneity of published studies
Design bias	Inappropriate study design choice, inability to appropriately answer study aims with chosen study design	Quality assessment and critical appraisal of included studies
Linguistic bias	Overrepresentation of English, or other dominant languages in the literature	No restriction on language of publication for inclusion in review
Temporal bias	Favouring of newer publications / study results in reviews	No restriction on date of publication for inclusion in review
Confounding	Confounding variables influencing dependent and independent variables, leading to spurious associations	Quality assessment and critical appraisal of included studies (215, 217-219)

3.4.3 Literature searches

For my reviews, seven databases; Ovid MEDLINE, Embase, Web of Science, Current Nursing and Allied Health Literature (CINAHL), British Nursing Database, Cochrane CENTRAL, and PsycINFO (222-228), were searched. Searching multiple databases is recommended, as limiting to one or two main databases does not provide a thorough summary of the existing literature base, particularly when searching for specialised topics (229-231). Therefore, due to the multidisciplinary nature of malnutrition, more specialist databases, including nursing databases (CINAHL, British Nursing Database), multidisciplinary databases (Web of Science) and biomedical databases (Embase) were searched alongside broader medical databases (MEDLINE, Cochrane) (222-227). To complement the searches, forward and backward citation searching of included studies, a type of snowballing, often referred to as chain searching, or mining (232), was also conducted. This ensures a comprehensive search, and is particularly useful for identifying newer publications that have cited other works, which may not be well indexed in bibliographic databases (233). Recent reviews suggest that citation tracking, or forward and backwards citation searches identify up to 8 – 12% unique references not found in database searches (234-236).

3.4.4 Quality assessments

The assessment of study quality in a systematic review, with a lower weighting of results given to lower quality studies, is a key aspect of a systematic review (212). Many tools for appraising study quality exist and vary by the design of the study being assessed. These include the Critical Appraisal Skills Programme (CASP) checklist for cohort studies (237), the Appraisal tool for Cross-Sectional Studies (AXIS) (238), or the Newcastle-Ottawa Scale (NOS) for assessing non-randomised studies (239).

For the first review, the CASP checklist points one to 10, were used (237), see **Appendix 3** for CASP questions. The CASP checklist covers aspects that are appropriate to assess all study designs identified by the review, e.g., appropriate for participant recruitment, or accuracy of measurement of exposure. Secondly, 38 of 42 included studies were cohort studies, which favoured a cohort-based checklist. Separate checklists for cross-sectional study designs, such as the AXIS (238), or the NOS (239) could have been used, but their content was not comparable to the established CASP cohort study tool, and the use of multiple tools would have made comparing study quality difficult. Similarly, for the second, mixed-methods review, a newer multi-study design checklist, the Mixed-Methods Appraisal Tool (MMAT) was used due to the inclusion of both quantitative and qualitative studies within the review (240).

3.4.5 Analysis of results

For this thesis, several methods of analysis of systematic review results were employed. For the systematic review of the literature addressing the relationship between markers of malnutrition and outcomes in older adults with cancer, a combination of meta-analysis, narrative synthesis, and thematic analysis was used to synthesise the literature. For the second review, a mixed-methods review investigating patient, family and carers views and experiences of malnutrition screening, both narrative synthesis, and thematic analysis were used. The use of these methods are discussed below:

3.4.5.1 Meta-analysis

Meta-analyses, the statistical synthesis of study results (215), was conducted with two makers of malnutrition, detailed in **Chapter Four**. Meta-analyses combine data of included studies whilst accounting for within and between-study variance (215). Studies are weighted based upon their variance; how scattered the data are (215), with studies with large variances, and small sample sizes, typically contributing less to the overall estimate of effect (241). For my first review, a minimum of three studies, with adequately comparable populations and outcomes, were needed to conduct a meta-analysis. Although there is no fixed number of studies required to conduct a meta-analysis, the larger the number of studies, the higher the quality, the smaller the effect study heterogeneity will have on the outcome (218, 241).

Heterogeneity refers to the amount of variability seen between studies (218). Within meta-analyses, a decision regarding whether to use fixed or random-effects models must also be made. A fixed-effect analysis assumes that all studies are estimating the true treatment effect size, whereas random-effects models allow for differences in treatment effect sizes between studies to be seen (242, 243). This relates to the cause of heterogeneity, with fixed-effect models assuming any differences in effect size are due to sampling error, whereas random-effects models assume differences in effect size can be due to either sampling error or heterogeneity (242, 243).

To determine which model to use, the I^2 statistic, which measures the percentage of variation that is due to heterogeneity (244), was used. If little heterogeneity is seen, a low I^2 percentage is given, and a fixed-effect model can be used, conversely, if significant heterogeneity exists, a high I^2 percentage is seen, and a random-effects model is indicated (244). There is some argument that small meta-analyses may bias the results of the I^2 statistic, producing overestimates of heterogeneity (244). Because of this, set guidelines regarding thresholds for when to use fixed or random-effects models based on I^2 have not been set, and subjective interpretation of thresholds is encouraged (243, 244).

Meta-analyses are not always appropriate, particularly if studies are heterogeneous, for example, if the outcomes, participants, or interventions are not comparable; their inclusion and synthesis would provide meaningless results (241). Instead, a narrative synthesis of study results taking into account study quality to summarise results (215), would be more appropriate. Narratives syntheses were completed for the majority of study outcomes where meta-analysis was deemed inappropriate. Similarly, in reviews where meta-analyses are not possible, such as with the second review, where qualitative data will be assessed, conducting a narrative synthesis of quantitative results is most appropriate.

3.4.5.2 Narrative synthesis

Narrative synthesis is an approach that maps and synthesises multiple studies to provide an initial descriptive summary and explanation of the characteristics of the included studies (211, 245). Like a meta-analysis, narrative reviews produce an analysis of the outcomes of interest within the study, but instead follow a text-based, rather than a statistical approach (245). Narrative reviews are a more subjective method than a meta-analysis, therefore a rigorous quality assessment, see section **3.4.4**, is required (245).

A three-step approach for the narrative synthesis was used to synthesise the evidence in the reviews, these steps were; i) preliminary synthesis of results, ii) exploring relationships between studies, and iii) assessing the robustness of the synthesis (245). To undertake this, the results of each study were be tabulated, grouped, and described.

3.4.5.3 Thematic synthesis of qualitative data

Several methods of data synthesis, such as a realist synthesis, narrative synthesis, or thematic analysis could have been used for the qualitative systematic review data (198). The role of a narrative synthesis has previously been discussed, see above section **3.4.5.2**, and although useful for summarising data, it was not appropriate to meet the aim of the second review, regarding patient's experiences of nutritional screening, as narrative syntheses are more descriptive, rather than theory-building (198). (198). Conversely, a realist synthesis is a very iterative, theory-driven process (198, 246). However, realist syntheses are aimed at developing a deeper understanding of an intervention, through the formation of context-mechanism-outcome (CMO) hypotheses, to provide an explanatory analysis (246). However, this approach would not address the aim of my research question.

Thematic synthesis is a commonly used method of synthesising qualitative literature, as described by Thomas and Harden (247, 248). The aim of thematic synthesis is to identify commonalities and differences in qualitative literature, and synthesise these results (247). The use of thematic synthesis, and its structured format, work well with mixed-methods research:

Its defining output is the summarisation of data using a systematic format, which is reproducible, and has been described as almost 'auditable' in its process (247, 249). This model also works well with the format of qualitative or mixed-methods systematic reviews; as a systematic and methodological analysis of the qualitative research is conducted, searching for patterns, with the aim of producing a detailed description of the themes and content of the papers (247, 249).

3.4.6 Application to thesis

The systematic reviews within this thesis were designed to address two important aims, and the findings of which informed upon aspects of the observation study. Primarily, the systematic review of markers of malnutrition informed upon the anthropometric measures and questions used to assess malnutrition in the study patient-participants. This review also aimed to determine the relationship between markers of malnutrition and clinical outcomes in older adults with cancer. Similarly, the review of patients' experiences and views of nutritional screening was used to both inform the study topic guide for qualitative interviews and advised regarding the acceptability and utility of nutritional screening. Systematic reviews were chosen over other forms of reviews, such as narrative or scoping reviews, due to the specific and narrow nature of the topics being addressed, and the requirement to minimise bias, and produce a comprehensive summary of the available published evidence. Multiple methods for the analysis of the data gathered by the systematic reviews were possible, and their uses in this thesis have been discussed, including appropriate use of meta-analysis, narrative analysis, and analysis of qualitative data using thematic analysis.

3.4.7 Observational study

An observational cohort study was planned as part of this thesis, with the aim of addressing the research questions; i) which markers of malnutrition, sarcopenia, and cachexia, used in screening tools are predictive of clinical outcomes in older adults with cancer, and ii) what is the acceptability, and clinical utility, of a single screening tool to detect malnutrition, sarcopenia, and cachexia, in older adults with cancer. Due to the challenges imposed by the pandemic, and the impact of COVID-19 upon participant's health, and hospital admissions, discussed in section **6.7**, it was not appropriate to use the data gained from longitudinal aspects of the cohort study. The following sections discuss the choice of study originally planned, with the impact of moving from an observational cohort study to a cross-sectional study also delineated.

Although randomised controlled trials (RCTs) are the gold standard for clinical research (250), the research aims would not be able to be met through a RCT. For this study, the impact of an

intervention is not being investigated, I am investigating the diagnoses of malnutrition, sarcopenia, and cachexia, their commonalities, predictors, and disease-related symptoms, which an RCT study design would not address. A central part of my research was to investigate which variables associated with the three conditions being investigated are predictors of clinical outcomes, and which variables are predictors of the conditions themselves, and for this, an observational study design was most appropriate (250-252).

3.4.7.1 Types of cohort study

Several types of cohort studies are possible, these include; preliminary, derivation, or validation studies (252, 253). A derivation study could have been used for this thesis, whereby the outcomes of interest; the development of malnutrition, sarcopenia or cachexia, would have been studied retrospectively to identify potential facets of disease which may predict their development (253). However, this relies upon accurate retrospective data documentation (253). For the conditions of interest, the required information e.g., historical weight loss, assessments of function, and anthropometric tests, are either not routinely tested or consistently recorded in clinical practice. Additionally, derivation cohort studies are at a high risk of confounding, risking spurious associations, therefore results cannot be relied upon to inform the production of a shortened screening tool, if the produced tool were valid to use in clinical practice (253). Similarly, a validation cohort study cannot be conducted. A validation study, which tests a model produced during a derivation or preliminary study, would assess a tools wider applicability and usability in clinical practice (253, 254). However, no single tool has yet to be produced, therefore this cannot be conducted.

For this thesis, a preliminary observational cohort study was planned, over a derivation or validation study. A preliminary study was chosen as I wished to determine the first steps of whether it is feasible, acceptable, and clinically useful to screen patients for the conditions of interest, simultaneously, in a clinical setting (254). Both qualitative and quantitative methods are often employed in preliminary studies, to allow triangulation of study results, and to determine the acceptability of the proposed intervention (193, 254). As preliminary studies are conducted prospectively, there are opportunities to explore confounding, and ensure appropriate relevant data are collected (254).

Preliminary studies are often undertaken to refine an intervention and evaluate its acceptability, feasibility, cost of undertaking, and study uptake, all of which are key for determining if larger studies can be conducted (253, 254). Preliminary studies can also provide necessary data to determine appropriate sample sizes for validation studies, such as data on the prevalence of the conditions, or on study attrition rates (254).

3.4.7.2 Cross-sectional

Due to the impact of the pandemic, it was not appropriate to use many aspects of the longitudinal data gathered during the cohort study, See section **6.7**. Therefore, cross-sectional data, gathered at the start of the pandemic, which was less likely to be affected by the impact of COVID-19, was used.

Cross-sectional studies, like cohort studies, have both strengths and weaknesses. Cross-sectional studies are defined by their use of data gathered from a population at one specific time point (255), and have historically been used to understand the prevalence of diseases in clinical research (255), measuring both the outcome and the exposures in a study population, at the same time (256). However, as data are gathered at one set timepoint, it is not possible to attain causal relationships between exposures and outcomes, only associations (256), and data must be interpreted cautiously due to this (255). Cross-sectional studies are also unable to measure the incidence of outcomes, and are not an efficient method for studying rare diseases (252, 255). The conditions investigated in this study are however known to be common in older adults with cancer (12, 13). Therefore, robust estimates of prevalence would likely be possible from a smaller sample sizes, as compared to rare conditions, where either a larger sample size, or studying of participants already known to have the condition(s), would be required (252, 255).

Cross-sectional studies are also useful for studying multiple outcomes, with data only collected once, posing a minimal burden on participants (252). Cross-sectional studies are often conducted prior to cohort studies, during the planning stages or at baseline in a cohort study (256), as was conducted here, with cross-sectional studies providing baseline initial associations of interest, which can then be further explored in studies that are able to control for confounders (255, 256).

3.4.7.3 Application to thesis

The original aim of this thesis was to produce a screening tool able to predict patient outcomes, and the observation of predictive variables against specified outcomes was key to the production of this single screening tool. For this, an observational study, able to examine relationships, and the predictive abilities of these relationships in determining key clinical outcomes, was chosen. Observational studies aim to identify and assess factors that influence disease or health outcomes, with cohort studies offering the benefit of observing temporal relationships between exposures and outcomes (257). A cohort study was originally chosen over a cross-sectional study due to the requirement to observe outcomes over time. Observational studies can also provide estimates of prevalence, and have increased ability for statistical measures of risk, with hazard and odds ratios able to be calculated (251).

Although cohort studies are time intensive, and require significant follow-up periods, their ability to control for multiple confounding factors, and ability to assess multiple exposures and outcomes in the same population, made their design appropriate for my research question (251). The use of an observational cohort study design was appropriate as the conditions being investigated are common in the population being studied. If the conditions were rare, case-control, or retrospective observational study designs may have been required (251, 258), but with the inherent limitations of poor documentation of the variables of interest; as information regarding investigated variables, such as measures of muscle mass, or recordings of appetite, are not routinely collected, a retrospective study was not appropriate.

Although not originally planned, the use of a cross-sectional design, as a mitigation for the impact of the pandemic, did mean that prevalence estimates for each of the conditions could still be obtained, and initial predictor variables for each of the conditions could also be investigated, to address the modified study aim to gain exploratory estimates of the prevalence and overlap of the three conditions in older adults with cancer.

3.4.7.4 Sampling methods

For the observational study, several methods of sampling were considered. Random sampling, where each participant has the same probability of being selected into the sample (259) could have been completed by numbering each participant, using random number tables, or stratified sampling, to select participants (259). Stratified sampling; where a population is divided into groups, based on demographics, with recruitment of participants equally from each group (259), could also have been used. Stratified sampling is often used when hoping to sample minority populations, to ensure participants are adequately represented within the sample (259). Due to the available resources for this study, stratifying each patient attending the Queens Centre of Oncology and Haematology (QCOH) centre would not be possible, given the number of patients, and single researcher.

Consecutive sampling, of approaching all participants who meet the study inclusion criteria (259), would be appropriate for use in this study, however, as with stratified sampling, due to the time and resource limitations within a PhD thesis, sampling all participants who meet the inclusion criteria would not be possible. Convenience sampling, of recruiting easily accessible patients, was also an option, however, this approach is liable to introduce bias (259). Although this method is comparatively easy, and commonly used, biases, mainly selection bias, where the study population differs from the population of interest can occur (259). This would mean that study results may not be generalisable to the wider population (259).

For this study, patients who were eligible for inclusion, based upon the study inclusion and exclusion criteria, see section **6.6.2**, were approached during the recruitment period. This approach was chosen with the aim of minimising selection bias, from only recruiting through a convenience sampling approach (259), however, not all patients who were eligible were approached, due to time and researcher constraints.

It is important to note that the risk of sampling bias is a known issue in this population, of finding patients who are both available and willing to be involved, the risk of 'healthy volunteer bias' (260), and gatekeeping; whereby more unwell, distressed, and older patients are less likely to be approached (261, 262), may all bias the sample.

To minimise the risks of, and aid identification of biases as discussed above, the characteristics of the sample were considered. To assess the representativeness of the sample attained during the study, a comparison sample, gained by completing a census of all adult inpatients who meet the inclusion criteria, at QCOH, during a five-day period, prior to study commencement, was documented. Key demographics of the population, of; age, sex, and cancer diagnosis, were documented and compared to the final sample achieved. The use of regression analysis, an adequate sample size, and researcher awareness of the above bias risks were planned to help control for these biases (260, 261).

3.4.7.5 Patient outcomes

In this study, the association between markers of malnutrition, sarcopenia, and cachexia and patient outcomes were being investigated. For this, many alternate outcomes could have been recorded, however, these were limited by the study design, feasibility, and the purpose of their collection. Key patient-centred outcomes, such as health-related quality of life (HRQOL), physical function, or body weight changes, could have been recorded (263). As discussed in section **6.6.3.1**, due to the study design of a planned single contact with participants, this meant that any outcomes collected must be consistently recorded in patients' notes, and not require additional patient contact to retrieve. Additionally, consideration of commonly recorded outcomes, which were likely to be recorded for all patients, to minimise the risk of missing data, further limited the options. As this thesis follows a pragmatic paradigm, a pragmatic approach to outcomes were also taken, and considerations were made regarding what would realistically be recorded, what was efficient to collect, likely to be reliably documented, and what was well-understood as important outcomes to observe (264). Outcomes related to patient quality of life, quantity of health, and anti-cancer treatments, are relevant to both patients and clinicians (263), and are routinely documented. Due to the target study sample size, outcome frequency must also be considered, as uncommon outcomes would require larger sample sizes to see significant or clinically worthwhile differences (254).

From this, routinely recorded longitudinal outcomes, which are common in this patient population were decided upon, including; incidence of mortality, hospitalisation, hospital length of stay, anticancer treatment adherence, and anticancer treatment toxicity. Additional outcomes of referral to allied healthcare professionals (dietitians, occupational therapists, physiotherapists and speech and language therapists), due to their relation to the management of malnutrition, sarcopenia, and cachexia, and their clinical implications, were also recorded. As mentioned, due to the impact of COVID-19 on these outcomes, although they were collected, their use in the thesis was unfortunately limited, see section **6.7**.

3.4.8 Screening tool choices

As discussed in the introductory chapter, there are several screening tools available for both sarcopenia and cachexia, and a plethora of malnutrition screening tools. For the study, participants were screened for all three conditions using a selection of these tools. Their use, and selection, are discussed:

3.4.8.1 Cachexia screening tool

Three screening tools for cachexia, the CAchexia SCOre (CASCO), Mini CAchexia SCORE (MCASCO), and Cachexia Staging Score (CSS) (16, 55), see section **1.2.3**, were published before the start of the study. For the study, the abridged MCASCO was chosen over the CASCO or CSS.

The MCASCO was chosen over the original CASCO screening tool due to its reduced number of required measures, of 21 questions or measures, compared to 44 in the CASCO (16). Despite these reduced numbers, the MCASCO retains the psychometric properties of the CASCO (16). One concern with the MCASCO was that it was built on the general definitions for cachexia (22, 23), rather than the cancer-specific definition by the International Consensus (19). As discussed in section **1.2**, the use of Evans et al., 2008 definition may have a higher sensitivity for detecting cachexia, or may only identify later-stage cachexia (25). The other option for a screening tool, the CSS, a tool that only contains seven questions and three biomarkers, also requires an assessment by a clinician of the patient's functional status (55). Five of the seven questions in the CSS are the SARC-F screening tool for sarcopenia (109). Due to the issue of undesirable overlap between cachexia and sarcopenia, and the aim to distinguish one condition from another, I did not want to include sarcopenia screening in the identification of cachexia. Once the SARC-F was removed, only single questions regarding appetite and weight loss, a measure of performance status, and biomarkers, remain. In looking for markers of cachexia, using a tool with minimal other markers, particularly when many remaining markers overlap with malnutrition, did not seem logical.

Finally, neither the CASCO, MCASCO or CSS had been assessed for use in clinical practice, but the requirement by the CSS for a subjective clinician opinion may reduce the wider usability of the tool. For these reasons, the MCASCO, which includes multiple variables; inflammation, assessment of quality of life, physical performance, muscle mass and weight, and anorexia (16), was chosen.

The CASCO screening tool (54), and therefore the abridged MCASCO (16) tool, was developed based upon a published cachexia definition and diagnostic criteria (22), and was therefore designed as a diagnostic tool in itself. Therefore, for this thesis, MCASCO screening tool results will be used as an indicator of the presence of cachexia.

Since study commencement, other screening tools, such as the PG-SGA for malnutrition screening, have been suggested to detect cachexia (265). However, as with the CSS and overlap with sarcopenia, the use of a tool produced to identify malnutrition, used to detect cachexia, would further muddy the waters when aiming to distinguish between each condition.

3.4.8.2 Sarcopenia screening tool

As discussed previously, see section **1.3.5**, many screening tools for sarcopenia have been produced, including the Short Portable Sarcopenia Measure (SPSM), Ishii formula, Mini Sarcopenia Risk Assessment (MSRA) questionnaire, and the SARC-F and its subsequent algorithm suggested in the European Working Group of Sarcopenia in Older People 2 (EWGSOP2) consensus paper (17, 103, 104, 107, 109). When designing the study, the only screening tool which had been validated repeatedly, and in more than one population, was the SARC-F tool (109). For the other tools, only the construct validity of the SPSM had been examined, finding the SPSM was related to knee extensions and fear of falling, but its association with clinical outcomes had not been assessed (103). The SPSM was also developed in adults aged 49 – 65 at baseline, where the risk of sarcopenia is lower than in older adults (18, 72). The Ishii formula (104) and MSRA had both been validated in several small studies, however, both are based upon the EWGSOP 2010 criteria, which places less diagnostic weighting on muscle strength; a factor which has now been suggested to be a stronger diagnostic marker than previously thought (17), meaning the Ishii formula, based on calf circumference and hand-grip strength (104) and MSRA on physical and nutritional characteristics related to sarcopenia (107), do not correspond with the most recent diagnostic criteria.

The five question SARC-F tool, which has been incorporated into the algorithm in the EWGSOP2 2019 guidelines, has been validated in large-scale studies (110, 111), and has been

shown to be associated with patient outcomes, including hospitalisation and mortality (112). However it must be noted that the tool has a very high specificity, but poor sensitivity, resulting in a high false-positive rates (119). To manage this, the SARC-F algorithm, for diagnosing and quantifying sarcopenia, chapter one, **Figure 1** includes assessments of muscle strength and muscle quality or quantity to assess and confirm the presence of sarcopenia (17). For this, the SARC-F questionnaire is used to identify potential cases of sarcopenia, rather than to diagnose the condition (17). This combination of measures of muscle quality, quantity, and strength, as well as participant's daily physical function through the use of the SARC-F questionnaire, provide a complete sarcopenia assessment (17).

As with the CASCO and MCASCO screening tools (16, 54), the EWGSOP2 algorithm aims to identify and diagnose sarcopenia (17), with the tool built upon the international consensus definition of sarcopenia (69), with the variables and thresholds used within the tool currently used to diagnose sarcopenia and its severity (70, 71). Therefore, for this thesis, the EWGSOP2 algorithm will be used as an indicator of the presence of sarcopenia.

3.4.8.3 Use of Bioelectrical Impedance Analysis

Both sarcopenia and cachexia screening require measures of muscle quality and quantity (16, 17), with the SARC-F Algorithm suggesting the use of Computer Tomography (CT), Magnetic Resonance Imaging (MRI), Dual Energy X-Ray Absorptiometry (DEXA) or Bioelectrical Impedance Analysis (BIA) (17). For this study, BIA will be used. The use of CT within this study is not feasible: Although many patients receiving anticancer treatments receive a planning CT for treatment, inclusion of the L3 vertebrae, allowing cross-sectional assessment of total skeletal muscle area, , varies. Due to time and cost limitations, combined with increased radiation delivery and increase participant burden, performing additional CTs for this study is not feasible. A recent review (266) comparing analysis of low muscle mass in colorectal cancer patients found that use of BIA, compared to the reference method of measure of lumbar muscle cross-section by CT, showed similar prognostic values for survival. Additionally, the use of BIA in palliative care has been investigated, finding variation in body composition by gender, and cancer diagnosis and severity, as expected (267).

Another benefit in using BIA relates to time demands; per participant, the time required to complete an assessment of muscle mass using the BIA is less than 20 seconds, compared to 10 to 20 minutes for a DEXA, 15 to 30 minutes for a CT and 30 to 40 minutes for an MRI.

For this study, a portable Tanita BC545N BIA scale, which completes body analysis within 20 seconds was used, to allow measures of weight and muscle mass. Due to the use of mild

electrical currents, participants with pacemakers were excluded for measures using the BIA scale.

The MCASCO calls for comparison of historic against current muscle mass (16). As historic measures of muscle mass are not available, and repeat measures are not appropriate in this population, see section **6.6.3.1**, comparison of current skeletal muscle index against reference ranges for older adults were used in place of historic measures, with 2 standard deviations below the mean threshold for values of skeletal muscle index for the young reference group (268, 269).

3.4.8.4 Malnutrition screening tool

To determine which tool would be most appropriate to use to identify malnutrition in older adults with cancer, a systematic review of markers of malnutrition, was conducted. As discussed in section **1.5.5**, although many malnutrition screening tools exist, their content is variable, and many questions regarding their validity exist. Due to the results of the systematic review, rather than choosing a specific screening tool for malnutrition, questions used in malnutrition screening tools were asked. For this, values for all commonly used markers of malnutrition were gained, so that diagnostic test evaluations, to determine appropriate thresholds and the validity of each marker, in relation to participant outcomes, could be assessed. As all screening questions were asked, any screening tool could be populated with the answers to diagnose malnutrition. See section **6.2.2**, for malnutrition screening questions. For use in results analysis, population of three key malnutrition screening tools was conducted, of the 3-MinNs, identified as best meeting the ESPEN criteria for malnutrition (18, 178), the PG-SGA as the most commonly used reference standard for malnutrition (141), and for MUST, the most commonly used too in clinical practice (138, 158).

Unlike with the CASCO (54), MCASCO (16), and EWGSOP2 (17) screening tools, malnutrition screening tools often aim to identify 'risk' of malnutrition, rather than diagnose the condition itself. As discussed, the content and validity of these screening tools vary, and further investigation is required into the most appropriate screening tool to use to identify malnutrition in older adults with cancer. For the purpose of this thesis, the results of 3-MinNs screening tool (178), due to its alignment with the ESPEN criteria (18) for malnutrition, will be primarily used to identify malnutrition, with the impact of this discussed throughout the thesis.

3.4.8.5 Anthropometric measures

Additionally, for this study, anthropometric measures were taken. Each measure, its use, and current evidence for use are detailed in **Table 13**. The overlap of each anthropometric measure, for each condition, is noted. As I aimed to explore the overlap between malnutrition,

sarcopenia, and cachexia, the commonality of anthropometric measures used to diagnose the conditions must be highlighted. Several key anthropometric measures, such as body weight, mid-arm circumference and measures of fat-free mass, are used to diagnose malnutrition. However, each measure is also used as an indicator of cachexia, sarcopenia, or both (16-18), making differentiating between the three conditions in clinical practice more challenging.

Table 13: Study anthropometric measures

Anthropometric measure	Condition	Measurement(s) taken	Measurement uses	Evidence for use
Body weight (kg) loss	Malnutrition Cachexia	Current body weight in kg Previous or usual weight from a specified time point (patient reported)	Calculated percentage, or actual, body weight loss over a specified time period	Increased risk of morbidity (post-op surgical, during oncological treatments; treatment toxicity, falls, delayed wound healing, functional impairment) and mortality (8, 153, 156, 161-163, 270)
Body mass index (BMI) (kg/m^2)	Malnutrition	Current body weight in kg Height in metres	Weight (kg) / height $(m)^2$ Estimation of body fat	Common clinical indicator, validated predictive value, noted can be disingenuous in obesity, with age, sex, physical activity, disease status and physique not considered (140, 271)
Mid arm circumference (cm)	Malnutrition Sarcopenia	Mid-point of acromion and olecranon process (shoulder to elbow) of non-dominant arm. Measure around arm.	Estimation of BMI Proxy measures of low fat-free mass	Used as a proxy measures of low fat-free mass (272), may allow estimation of body weight; mainly used in children, some evidence in adults (273). Shown to be inversely associate with all-cause mortality in non-obese (274)
Handgrip strength (kg)	Malnutrition	Measure of static force generated by the hand around a dynamometer	Indicator of muscle strength	Possible predictor of nutritional status (275). Variability in methods of assessing grip strength; consistency required (276, 277).

	Sarcopenia			Associated with mortality risk in cancer patients (278), with lower grip strength associated with all-cause mortality and multi-morbidity in adults (279)
Fat free mass (FFM)	Malnutrition Cachexia Sarcopenia	Weight, fat mass and fat free mass using bioelectrical impedance analysis (BIA) Height in meters	Body composition measure FFMI = $\frac{\text{fat – free mass}}{\text{height}^2}$	Fat-free mass; varies by age, height, sex, and disease status. Measure includes all internal tissues, bones, and water (280)
Appendicular skeletal muscle (ASM)	Sarcopenia	Sum of muscle mass of all limbs, measured using BIA	Body composition measure of the sum of all four limbs	Reflective of body muscle mass, accounting for >75% total skeletal muscle (281). Used to estimate muscle quantity, nut may need to be adjusted for height, weight or BMI (17)
Skeletal muscle mass	Sarcopenia	Skeletal muscle mass measured using BIA	SMI = ASM / height^2	Skeletal muscle mass measured using ASM or whole body SMM using BIA recommended for use as measure of muscle mass for sarcopenia (282)
Chair stand test	Sarcopenia	Number of sit to stand repetitions over a specified time (30 seconds)	Proxy measure for strength of leg muscles	Measure of muscle strength for sarcopenia (17, 283, 284). However, may be influenced by physiological and psychological factors, including vision, body weight, pain, anxiety (285)
Timed up and go test (TUG)	Sarcopenia	Timed rise from chair, 3-metre walk, turn, walk back, and sit in chair	Evaluation of physical function	Measure of physical performance for sarcopenia (17). Due to simplicity can be performed in clinical settings (286). High interrater reliability (0.97) (287).

3.4.9 Quantitative data analysis

As outlined above, a large number of variables were collected for this study, including baseline demographics, medical diagnoses, biochemical markers, results of individual components of the screening tools, and patient participant outcomes, such overall survival, hospital admissions and associated length of stays. Section **6.2.1**, describes the data collected. As large volumes of quantitative data were to be collected, considerations of the methods for managing and analysing data were essential prior to data collection.

Several options were considered for the management of the data, of both the initial collection, and analysis. A data management plan, see **Appendix 4**, was constructed prior to data collection. For face-to-face data collection with patient participants, either electronic or paper records for data collection could have been used. Multiple data sources were being used to collate data, including: patient report, Hull University Teaching Hospital's (HUTH) patient record system Lorenzo, the oncology information system ARIA, and recordings of study anthropometric measures, including BIA readings and hand-grip strength measures. This, coupled with the variety of potential settings for data collection, meant it was decided that paper forms, which were more portable, convenient, and ensured permanent recording of each measure, were used for the initial data collation. These paper records were then transcribed punctually onto an electronic database. An electronic database compatible with appropriate statistical software was required, therefore Microsoft Excel was chosen.

The methods of data analysis were originally designed based upon the expected sample size estimate of 120 patient participants completing the quantitative measures, with data analysis methods discussed in section **6.3.5**. The original data analysis plan, and sample size, were feasible based upon the first eight to 10 weeks of data collection. However, due to difficulties in recruitment caused by the COVID-19 pandemic, and a substantial drop in recruitment rates, the methods of data analysis were changed to be appropriate for the sample collected. Section **6.7** discusses the changes required due to the problems encountered due to the COVID-19 pandemic, including how the study, including methods of data analysis, were modified.

3.5 Qualitative methods

A defining feature of qualitative research is its ability to focus on 'lived experience', and 'the words' used, over quantitative research which focuses on the 'numbers' collected and data to be analysed (191). Qualitative research also produces an opportunity to understand data from the participant's perspective, rather than as a clinician or researcher. The impact of these differing roles is discussed in section **6.6.6**. Although qualitative research allows in-depth exploration of a topic with small sample sizes, and can explain complex research in a way not possible with quantitative measures (288, 289), several limitations must be considered and addressed. Primarily, the risk of bias, or risk of lack of rigor and trustworthiness, and difficulties regarding quantification in qualitative research (290). A summary of factors that can introduce bias into qualitative research are detailed in **Table 14** along with the methods employed for their management within this thesis.

Table 14: Sources of bias in qualitative research, and their management

Source of bias	Biases	Management of bias
Sampling	Unrepresentative sample, challenges recruiting 'hard to reach groups', volunteer bias	Acknowledgement of biases in sample, structured sampling techniques
Researcher influence	Subconscious influencing of results, or data analysis	Recognising and accounting for personal biases. Use of reflexivity. Documentation of researchers own values and opinions. Maintaining clear decision trail in data analysis. Engaging with other researchers. Data triangulation
Response bias	Hawthorne effect: where participants alter their behaviour or answers due to their involvement in a study	Appropriate sampling. Considering role of the researcher, and participant relationship with the researcher
Researcher skills	Leading to procedural bias	Skill development, reflexivity. Engaging with other researchers (288-290)

3.5.1 Qualitative study design

Several aspects must be considered when designing a qualitative study. With qualitative work, research questions are often broad, and open-ended, allowing for unexpected findings, depth of answers, and richness of data (198, 291). However, to process this, aspects including the methods of data collection, the 'lens' in which to observe the phenomena being studied, and the method of analysis must be considered (198, 291).

3.5.1.1 Qualitative approach

In qualitative research, the theoretical perspective – the lens through which we observe the data – alongside the ontological and epistemological approach used, must be considered. As discussed in **3.1** this thesis follows a pragmatic philosophical approach, as well as using a mixed-methods study to answer the research questions. Therefore, when conducting the qualitative aspects of this study, an approach that melds with these considerations must be used.

There are several approaches by which qualitative data can be observed, these include, but are not limited to; using grounded theory, ethnography, inductive description, and phenomenology. In deciding which qualitative approach to utilise, two key contributing factors must be considered; i) using a lens appropriate for the research's pragmatic approach, and ii) ensuring the most appropriate lens to answer the research questions.

A pragmatic philosophical approach, with the aim of producing 'useful knowledge', grounded in reality (195), was chosen, among other reasons, due to the mixed-methods nature of the research. A qualitative methodology that fits within this paradigm is essential. Options such as inductive descriptive methodologies, which marry with objectivist or positivist epistemologies (198), would not have been appropriate due to their requirement for empirical 'factual' or 'objective' data (198), which although empirical data are being developed in this study, they will not be attained from the qualitative interviews. Similarly, at the opposite end of the methodological spectrum, use of critical theory, or postmodernist methodologies, which follow a creative, or critical more idealist ontology and epistemology (198), would also not have been appropriate to answer the research questions addressing prevalence and clinical utility.

A pragmatic approach can be considered the middle-ground between realist and idealist ontologies, therefore using a pragmatic approach allowed some flexibility regarding the methodological lens used (198). However, as pragmatism encourages findings that have 'real-world' value, and present findings in accessible, approachable, and actionable terms (193, 195,

198), this limits the methodologies down to those such as grounded theory, phenomenology, or ethnographic methodologies (198).

Grounded theory, which focuses on the interpretation of meaning, is useful for generating new hypotheses from data (198). As grounded theory is a structured but flexible methodology, it would have fit with the mixed-methods study design (198). Grounded theory methodology is most required when very little is known about the phenomena, and where an explanatory theory is needed (292). However, the use of grounded theory was not appropriate for this thesis due to the questions being posed, and with a focus on understanding participant opinions and views, other methodologies held more benefit. As grounded approaches, with a focus on the development of theories, would not provide the required data on participants' views and thoughts regarding screening (193, 289).

An ethnographic approach, which aims to develop intimate interpretive understandings of a topic (198), would have provided a description of the culture of nutritional screening, and provide an understanding of participants involvement in screening. However, ethnography would not have provided the depth of knowledge required to refine a screening tool, or gain information regarding participants' views of the process (289), and often follows a more abstract, or narrative approach than what is required to answer the posed research questions.

Therefore, the option of following a phenomenological approach was considered. Phenomenology is an appropriate method to use in mixed-methods research due to its focus on maintaining a strong and orientated relationship to the phenomena, or the primary research aim, which is achieved by maintaining an acute awareness and focus on the aim, in the context of the research (293). Also, the research question addressed by the qualitative interviews relates to participants' views and experiences of screening, which, following a phenomenological approach, would enable the analysis to be targeted towards these questions of 'what' and 'why', which is more readily asked using a phenomenological methodology (294).

3.5.1.2 Application to thesis

A phenomenological methodology, investigating participants lived experience, and their interpretations, was used when gathering qualitative data. This approach was used during face to face or telephone, one-to-one, semi-structured interviews for patient participants. A phenomenological approach was chosen over others, such as grounded or ethnographic approaches, for several reasons. Primarily, the focus on experience, and the ability to question 'what' a participant's experience was, and 'why' they may have experienced something in that way (294), favoured this approach. It is the focus on personal perspectives and interpretations

(293, 295), which makes phenomenology most appropriate in answering this thesis' research questions. Understanding participants' views and experiences will provide important data regarding the acceptability of screening, and the feasibility of the study measures. The use of phenomenology would also have been essential for the initial assessment of the tools face and content validity, particularly clinician and patient participants' views on the clinical utility of the tool, as per the thesis' original aims.

3.5.2 Data collection

There are several core methods for collecting data in qualitative research, all of which have their strengths and their challenges (291). These can be broadly categorised into three methods, of; interviews, focus groups, and observations (291), which are discussed:

Most commonly, interviews with participants are the primary method for collecting data in qualitative studies (291). Unlike a standard interview, where data amenable to quantitative analysis is generated, qualitative interviews aim to gain rich, in-depth data (198). There are several forms of interviewing techniques that may be used, these can be divided by their structure, of; i) open, also known as unstructured, ii) semi-structured, or, iii) structured, also known as rigidly structured interviews, which border on standard interviews (291).

Unstructured interviews are often based on a single question, with an open conversation around that question (296). This method provides a much more narrative enquiry, useful for investigating broad topics, and is more often used in ethnographic research (198). The use of a single, or very few, or unplanned questions, allows the participants to express their opinions in their own way, and focus upon topics important to them (198, 297). However, the researcher can have little control over the topics discussed, and unstructured interviews are generally used in long-term fieldwork (297, 298). Semi-structured interviews provide a more focussed conversation than an unstructured interview, providing the researcher with more control of the topic discussed, whilst inviting open-ended answers (289). Structured interviews provide control for the researcher regarding the topics discussed but risk a loss of depth of response by participants, with the questions encouraging closed answers if the researcher is not skilled in leading qualitative interviews (289, 296).

To mitigate this, the use of topic guides, with suggested 'prompts' to guide the conversation, rather than asking closed questions, can be used to encourage a narrative response from the participant (198). It is important to consider pilot testing interview guides, to see how effective chosen open questions and prompts are in eliciting the required information, without influencing the participants' answers (198).

Another method of gaining data for qualitative studies is the use of focus groups; a method by which a facilitator (the researcher), moderates a group discussion to generate research data (198, 291). Focus groups are a commonly used method in healthcare, as they can be an efficient and flexible method of gaining rich data from multiple participants simultaneously (198). Additionally, focus groups can result in a greater level of debate, leading to richer data, and allowing the researcher to step back from the conversation (198, 291). Despite these positives, without appropriate moderator skills, and considerations for group composition, focus groups can be challenging for the researcher to manage, and may result in off-topic discussions or dominant participants; resulting in inadequate data and missed participant views (198, 291). To mitigate these factors, purposive sampling, encouragement of all participants to express their views, and a clear topic guide may help (198, 291).

Finally, participant observation, of gathering data by observing and/or participating in a groups day-to-day activities, can be employed (198). This is particularly useful in health research and clinical practice, as it can allow researchers to document 'what happens', and allow researchers to evaluate processes and procedures 'in action' (198). However, observational data collection is at risk of observer bias, and this observation can result in a change in the actions of those being observed (291).

3.5.2.1 Recording and transcribing interviews

Several methods for documenting and collating data produced by qualitative interviews can be used, these fall broadly into two categories: written notes, and recordings.

Recordings, using voice recorders or film, provide the researcher with a precise record of the conversation, which can be transcribed into a text copy of the interview (191). The main benefit of recording is that it allows the researcher to focus on the conversation, rather than dividing their attention between note-taking, listening to, and observing, the participant (191). This lets the researcher focus on the nuances of the participants' answers, to pick up and explore relevant points. Voice recording is a common method of recording interviews (198). Video-recording interviews can capture non-verbal communication, however, this information is time-consuming to categorise and analyse, and requires interpretation by the researcher, which may lead to supposition (289). Instead of this, a reflexive study journal with notes made after the interview, of key points or non-verbal makers, can be kept.

Although transcription of the interview can be a time-consuming process, transcription by the research allows immersion within, and familiarisation of the interviews, a key process of analysis (299). Recordings can be transcribed 'verbatim', which involves replication of all verbal communication, with the inclusion of filler words, pauses, and emotional utterances (e.g.,

sighs), to increase the accuracy of the transcription (299). Verbatim transcription is recommended when following a phenomenological approach as it facilitates data analysis by bringing researchers closer to the data, increasing the validity of the data, and allowing less interpretation or misunderstanding of the data (299). Transcription can be thought of as an interpretive activity, which opens the process to researcher bias, therefore additional verbal communications which provide context will help reduce inaccurate interpretation (299). For this study, voice-recording with verbatim transcription was used.

3.5.2.2 Interview sample size

There are several considerations to be made when deciding on sample size for qualitative interviews. One of the main discussions is regarding if the aim is for data saturation; the point at which no new data emerges from further interviews (300, 301), or information power; where the more information a sample holds, the smaller the required sample size (301). Traditionally, data saturation, relying on a constant-comparative method, whereby interviews continue until no new themes emerge from the data, has been the primary method of determining sample size (198, 300, 301), with initial estimates of sample size drawn from similar prior research (198, 300). However, when to draw this line is often poorly described (301), and some argue that 'no new information' is a fallacy, as there will always be new insights with new data (300, 302). Instead, a focus on 'information power' may be more helpful; where the sample size is determined more by the level of information held by the participants, and its relevance to the study aims (301). For this, several considerations have been posed by Malterud et al., (301) which include; i) the scope of the aim of the study, if it is narrow (requiring a smaller sample size, or broad, requiring a larger sample size), ii) the sample specificity, if participant characteristics and experience relate closely to the study aim or not, as the denser the sample specificity, the smaller the required sample size, as there is likely to be less variation, and iii) the expected quality of dialogue, in this instance my ability as the researcher to speak knowledgeably regarding the interview topics, and my ability to conduct qualitative interviews successfully.

Additionally, the generalisability of the findings must be considered when determining sample size, as some argue that a smaller sample size, with limited participant variability, restricts the generalisability of the findings (303). Although generalisability of findings is often more associated with quantitative data, it is often seen as a limitation in qualitative research (303). This more statistical way of viewing qualitative data, of a small sample size equating to reduced generalisability, is not appropriate for qualitative research (198, 303). Instead, the representational generalisability, or transferability, of the qualitative research; where the similarities of the research can be compared looking at the context, rather than the research

topic, to determine if findings are transferable, may result in findings being generalisable despite a smaller sample size (303).

3.5.2.3 Application to thesis

For this thesis, semi-structured, voice-recorded, face-to-face or telephone interviews, were used, with data transcribed verbatim, with the sample size to be determined by information power, rather than data saturation.

I chose interviews for several reasons; primarily, the topics being discussed focused on the participants' views, experiences, and opinions of the screening process, and of the three conditions being investigated. This data could not have been gained through methods of observation as these are topics unlikely to be raised in natural conversation. Interviews also provide the most direct route to obtain detailed and rich data (291). Similarly, semi-structured interviews were chosen as insights regarding very specific topics were being studied, which were unlikely to be discussed without prompts, but a depth of understanding was required which would not have been gained with structured interviews.

In semi-structured interviews, questions asked relate to core elements of interest, directing the conversation towards these, but allowing 'prompts', or questioning of specific points within these key topics (289). To maintain a similar format among all participants' interviews, a topic guide, with key questions and notes for prompts, were used, allowing the interview to be guided to stay on point, using a systematic approach, without restricting participant's answers (289). I chose interviews, rather than observation, as the format of data collection, as insights are required regarding very specific topics, which are unlikely to be discussed without prompts.

The interview structure is outlined in section **6.4.3**. The interview process includes three sections; the introduction, the question themselves, and the debriefing (289). Due to the nature of topics being discussed, which may be of a sensitive nature, or evoke emotions or memories regarding the participants cancer journey, an introduction and debriefing are essential for ensuring the participants wellbeing. The introduction provides an opportunity to check understanding, reaffirm consent, re-discuss confidentiality, highlight the participant's ability to pause or stop the interview, and answer any questions the participant may have (289). Similarly, the debrief allows the researcher to close the interview and bring participants away from the topics discussed, or refer participants to emotional wellbeing services at the hospital, if they have been affected by the interview and require additional support.

The qualitative interview sample sizes target was based upon information power, and were to be flexible, depending on the strength of the dialogue, and available sample specificity (301).

As the aim of the interviews, and the topics to be covered, were narrow, and as the sample specificity was dense, with all participants invited to interview having completed the measures for malnutrition, sarcopenia, and cachexia, this suggested that a smaller sample size would be appropriate to meet the criteria for adequate information power (301). Additionally, although I have limited experience as a qualitative researcher, with some qualitative interview training, I have many years experience as a clinician, working with older adults with cancer, and discussing many aspects of patients health, which are covered in the qualitative interviews. Therefore the quality of the dialogue should be strong (301), as my knowledge of this area is robust. Sample sizes for the qualitative interviews are outlined in **6.4.2**, and justified in section **3.5.2.2**.

3.5.2.4 Qualitative data analysis

Different methods were considered for the qualitative analysis, with several decisions required regarding the research approach (inductive or deductive), research framework, and the method of analysis.

There are various options for qualitative data analysis, including; narrative analysis, thematic analysis, and interpretive phenomenological analysis (IPA) (304). A narrative approach, whereby the stories participants have told regarding their lived experience are described (304), could have been used. However, although gathering data on participant experience is crucial for this research question, this approach does not allow for discussion of participants' views, and is more gauged for analysing 'events', and how participants discuss these events (304), which is not appropriate for this research. Furthermore, narrative analysis ties better with a critical theory approach, rather than a pragmatic approach (198) which this thesis follows. Both IPA and thematic analysis were considered. IPA, using a phenomenological framework, aims to explore participants' experiences in detail, exploring how participants make sense of their world, and understand 'what it is like' from the participants point of view (305). A second stage of IPA, of the researcher then interpreting how the participant makes sense of their world, is also involved (305). Whereas thematic analysis, a foundational method of qualitative data analysis, is a flexible method of data analysis that aims to find patterns within the data (198, 306). Thematic analysis' method, of identifying, analysing and reporting patterns, or themes, within data, follows a structured formula, but allows flexibility in terms of the theoretical position, as it does not require the researcher to follow an inherently realist or idealist ontology, and can be utilised along the scale from objectivist to creative epistemologies (198, 306).

From this, thematic analysis was chosen over IPA due to its flexibility (306). Although IPA's approach is phenomenological, the methodology, particularly the focus on the two-step

interpretation; of the participants experience, and then the researcher's interpretation of the participants experience, does not match with the research objectives, and may draw focus away from the participant's own experiences and views. Instead, the use of thematic analysis, based on descriptive phenomenology was used. Thematic analysis allows the flexibility to follow a pragmatic approach to the data, whilst viewing the data from a phenomenological perspective (307). Additionally, thematic analysis, in which qualitative data are grouped, categorised, summarised, and reconstructed into themes or patterns, complements the mixed-methods approach (289). Although the limitations in the use of thematic analysis in a phenomenological approach have previously been outlined; including its limited focus (308), there is a long history of using this combination (309), including in health research (310, 311), and a useful framework for when using the two together (thematic analysis of lived experience), has been recently outlined (307). The methods for undertaking this are discussed in section **6.4.4**.

Thematic analysis supports a pragmatic paradigm due to its structured and organised data analysis (312). Undertaking thematic analysis has been compared to producing an 'audit-trail' of data analysis, providing evidence of decisions made, and the rationale behind these decisions (249). Thematic analysis also works well with phenomenology, as it enables a deeper, more interpretative exploration of meaning, patterns, and experiences gained from the phenomenological approach (249, 289, 293). Finally, due to the flexibility in thematic analysis, either an inductive or deductive approach, or a mixture of the two, can be used during data analysis (249, 289). For this thesis, as the topics being covered are relatively understudied, an inductive methodology is more appropriate.

3.5.2.5 Feedback loop diagram

In addition to conducting thematic analysis through a phenomenological lens to explore participants' views and experiences of the screening process, a deeper understanding of the role of the three conditions in a patient's health pathway was also required, to further understand their experiences and how any issues could be addressed. A possible methodological approach to address this was systems thinking. Systems thinking is described as a 'holistic approach' to analysis, that investigates the interrelationships of different systems through a wider lens, and can be used to inform upon the determinants of health (313, 314).

Health systems are influenced by many factors, including social systems which influence health and wellbeing, clinical healthcare services, and internal and external feedback (314, 315). The three conditions being investigated in this thesis, and their causes and consequences, are vast and complex (12, 17, 23, 28, 151, 153). Therefore, a method that allows exploration of the sequences, relationships, and variables related to malnutrition, sarcopenia, and cachexia,

which impact upon a patient's cancer journey would be beneficial for understanding how patients' experiences develop.

Causal loop diagrams are a common tool used in systems thinking to produce an illustration which maps hypotheses of system structures, through linking variables through causal relationships (316, 317), which can be between health services and/or social systems (317, 318). Although I am not investigating a 'health system', or looking at 'causal' factors, using this form of thinking and the use of loop diagrams may allow illustration of the complex relationship and positive and negative feedback loops which influence participants' views and experiences of the three conditions (319).

Other tools, other than loop diagrams, for systems thinking exist, and include process mapping, which includes the use of flow charts, to document the process of sequential actions and responses, or innovation management, which includes in-depth interviews with key stakeholders to build an understanding of the performance of a system from multiple points of view (319). Loop diagrams were chosen over a more linear method for mapping, as, during thematic analysis, the complexities, and overlap of themes, the relationships between various themes were seen. This meant it was not possible to tell a linear story, and instead, a method was required that allowed illustration of positive and negative feedback loops, and the interaction of complex relationships (314, 319). Additionally, this work focused on patient experiences, feedback from additional stakeholders e.g., clinicians or commissioners, would also be required to conduct innovation management (319).

Core steps of conducting loop analysis include; i) identifying data sections for the arguments and their supporting rationales, ii) identifying the relationships between variables or themes, iii) producing simple diagrams to represent each theme and their relationships, and iv) merging the simple diagrams into a collective feedback loop diagram (317).

3.6 Synthesis of thesis results

For this thesis, several separate, but related, components have been conducted, with the aim of answering the research aim and objectives. Therefore, consideration of how to integrate the findings of each of these components, and to do so in a valuable and appropriate, is required. Many different methods of critical appraisal frameworks exist (320), and include; Dellinger and Leech, 2007 Validation Framework (321), the Pillar Integration Process (PIP) by Johnson et al., 2019 (322), the Joanna Briggs Institute approach for mixed-method systematic review (323), and Critical interpretive Synthesis (CIS) by Dixon-Woods et al., 2006 (324).

Several of these methods were considered when deciding on the most appropriate approach for how to synthesise the data for a quantitative systematic review, mixed-methods systematic review, and mixed-methods observational study, to be able to answer this thesis' research question. In particular, the Pillar Integration Process (322), Joanna Briggs Institute approach (323), and Critical Interpretive Synthesis (324).

PIP was initially developed to integrate quantitative and qualitative data, following a subtle realist epistemological view (322), and involves four stages of analysis, i) 'listing' raw data (quantitative e.g., statistical results, qualitative e.g. code), ii) 'matching' the quantitative data to the qualitative data, iii) 'checking' data for quality purposes and filling any gaps if possible, and iv) 'pillar building' of comparing and contrasting findings to develop a meaningful narrative.

The Joanna Briggs Institute method for mixed-method systematic review integration involves a 'convergent segregated approach', of conducting separate qualitative and quantitative data syntheses, followed by integration of both findings, with this method aimed to focus on reviews addressing questions of meaningfulness and/or experiences in qualitative research, and effectiveness in quantitative data (323). Although aimed at systematic reviews, this method could be modified to include primary data.

Finally, Critical Interpretive Synthesis (324), also originally designed as a method for systematic review analysis, aims to encourage a critique of the literature, including 'taken for granted' assumptions and concepts (325). CIS was developed for when theorisation of the evidence is required (326), and can be used to synthesise both quantitative and qualitative research simultaneously (327), and is orientated towards theory generation, whilst allowing a more flexible approach and methodology, compared to other more rigid methods (326), such as PIP (322). However, due to this flexibility, there is a risk of ambiguity, opening up potential researcher biases (326). Therefore a transparent and explicit process, which is clearly documented, must be conducted (326). CIS involves a two-stage process, of i) assembling

'synthetic constructs', of producing a reduced account of the context of all studies i.e., 'summing up', and ii) creating a 'synthesising argument' in a framework that represents each of the constructs and details the relationships between them (328). This more flexible, two-stage approach was chosen, over the multi-stage and more rigid PIP method, and a modified version of the CIS was used to synthesise the evidence from the systematic reviews and observational study to address the thesis' research aim and objectives.

For this thesis, the CIS methodology was modified though the inclusion of additional study designs within the synthesis. The process, of first assembling synthetic constructs, was completed for each aspect of the mixed-methods study, and for systematic reviews, with the second step, of synthesising the relationship between each construct derived from each study aspect (328), subsequently completed.

This allowed a flexible approach to synthesising the evidence from multiple study designs. To minimise the risk of ambiguity, key findings and constructs were tabulated, providing clear evidence of the stepwise progression of the synthesis.

3.7 Study limitations

For this thesis, certain limitations have been set. These have been further impacted by the COVID-19 pandemic, resulting in additional limitations and alterations to the planned thesis. These issues are highlighted throughout the thesis. The section below summarises the key study limitations, with further strengths and limitations of the thesis presented in section **10.6** of the discussion chapter.

Due to time and resource constraints, this study has only been conducted in a single hospital site in the North East of England. Because of this, the ability to generalise these results to other population demographics is limited, but given the exploratory nature of the study, this was not the aim. Similarly, the limitation to the four most common cancer diagnoses, plus head and neck and upper gastrointestinal cancers, will limit the generalisability of the results, see section **3.2.1**.

Other possible methods to measure lean body mass, in place of BIA, which could have been used include CT, MRI or DEXA. Due to practicalities, of financial cost of conducting these tests, clinical resources of the machines and feasibility, and ethics of conducting additional tests within this patient group, the use of a portable BIA machine, at a significantly lower cost, and time requirement was used, see section **3.4.8.3**.

One key limitation, which shall be discussed throughout the thesis, has been the impact of the COVID-19 pandemic on the research undertaken. The mixed-methods study was designed and implemented before the start of the COVID-19 pandemic, and although barriers to achieving the studies goals, including potential recruitment challenges, were considered; with recruitment targets and timeframes modified for if recruitment rates were lower than expected, the complications caused by the pandemic far outweighed anything I could have foreseen. As highlighted below, realistic timeframes within the PhD timescale placed an initial restriction on study recruitment, however, due to delays and having to close and reopen the mixed=methods study three times during the course of the pandemic, original plans and study goals were no longer attainable. Section **6.7** discusses the changes to the study design to mitigate the effect of the COVID-19 pandemic on the thesis.

A main limitation of this thesis relates to time restrictions. To complete the thesis within three years, limitations on study size, length of follow-up, and the scope of the thesis were imposed. Realistic timeframes for data collection, combined with pragmatic recruitment rates, were key variables in defining the study type, and in deciding on the methods of data collection and data analysis used. To allow completion in three years, quantitative and qualitative data collection were designed to run successively, totalling 11 months, with ongoing computer-based data

collection for 12 months after the last patient had completed study measures. Due to the fragmentation of the timeline caused by the COVID-19 pandemic (see section **6.1.2**), this became unfeasible.

Considering the participant inclusion and exclusion criteria, population demographics, and expected recruitment rates, gathering adequate data for a quantitative-only study, if psychometric analysis of data, including factor analysis were to be conducted, a sample size in the hundreds would have been required. Due to time constraints, and an initial expected recruitment rate of three to five participants per week, this was not feasible. Therefore, a smaller sample size, of 90 to 120 participants, placed limitations on the methods of data analysis used. This also further justified the requirement for a qualitative study aspect to complement this study, and provide data triangulation for if statistically significant results may not be produced due to the sample size. The use of qualitative data alongside the quantitative data results would also help determine the clinical significance of a result.

As the focus of the qualitative interviews was regarding participant views and experiences of screening, it meant that the interviews concentrated specifically on information that would contribute to the development of the single screening tool. As an iterative process was used for the topic guide and scope of the qualitative interviews, there was the opportunity to explore other aspects of participant views and experiences of the conditions, away from screening.

Similarly, the scope of the original research aim, and questions, were limited to focus on clinical utility, rather than statistical validity. Assessments of the single screening tools construct validity and predictive ability would have required a larger sample. Unfortunately, this was not possible within the timeframe of this thesis. Instead, initial assessment of the tools face and content validity was planned and was to be used to shape and refine the tool. However, again due to delays caused by the pandemic, this stage of the study was not completed.

Reflexivity, critical reflection of my role and self, is essential in health research (198). My positionality, as a researcher and as a dietitian is discussed in section **6.6.6**. Is it essential to acknowledge the effect that my personal values and views, as well as professional background can have on my research, including when recruiting participants, administering screening tools, and undertaking qualitative interviews. When completing all aspects of the study, I was careful to remain neutral; using interview topic guides and screening tool proformas to minimise the impact of my clinical and personal views on questions asked. This included using open-ended questions in qualitative interviews, and use of advanced communications skills, learned

through years of clinical work and additional communication training courses, to explore patients' perceptions in an objective manner. Ideally, completion of data collection by other researchers, to further minimise risk of bias, would have been conducted, however, due to resource and time constraints, this was not achieved. Therefore, inclusion of other health care professionals and researchers in data analysis, including researchers from other disciplines, for example when developing qualitative themes, help reduce risk of bias.

3.8 Summary

This chapter has discussed the methodology used in this thesis, including the philosophical approach, mixed-methodology, and the rationale behind the methods chosen. In the next chapter, the first of the two systematic reviews will be presented.

Chapter 4: Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis, and meta-analysis

4.1 Chapter introduction

This chapter presents the text of an article published in the European Journal of Clinical Nutrition in May 2020. The text used for this chapter is identical to that in the published article, except for reference numbers, table numbers and figure numbers. References have been included in the main reference section rather than at the end of this chapter. Additionally, online supplementary material is presented in the thesis appendices, with subsequent references to these changes in the text.

4.1.1 Author contributions

The idea for this research was conceived by myself, with aid from my supervisor Miriam Johnson. I conducted the search with specialist advice from Sarah Greenley. I performed data extraction, with 25% of data checked by PhD student Gordon McKenzie. I performed the data analysis. Lewis Paton provided specialist advice regarding the analysis. I wrote the manuscript. All authors provided critical comment which I addressed and incorporated into the final published manuscript which all authors approved.

4.1.2 Article reference

Bullock, A.F., Greenley, S.L., McKenzie, G.A.G., Paton, L., Johnson, M.J. (2020) Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis, and meta-analysis. European Journal of Clinical Nutrition. 74: pp.1519-1535.

4.2 Abstract

Malnutrition predicts poorer clinical outcomes for people with cancer. Older adults with cancer are a complex, growing population at high risk of weight-losing conditions. A number of malnutrition screening tools exist, however, the best screening tool for this group is unknown. The aim was to systematically review the published evidence regarding markers and measures of nutritional status in older adults with cancer (age ≥70).

A systematic search was performed in Ovid Medline, EMBASE, Web of Science, CINAHL, British Nursing Database and Cochrane CENTRAL; search terms related to malnutrition, cancer, older adults. Titles, abstracts, and papers were screened and quality-appraised. Data evaluating ability of markers of nutritional status to predict patient outcomes were subjected to meta-analysis or narrative synthesis.

Forty-two studies, describing 15 markers were included. Meta-analysis found decreased food intake was associated with mortality (OR 2.15 [2.03–4.20] p=<0.00001) in univariate analysis. Prognostic Nutritional Index (PNI) was associated with overall survival (HR 1.89 [1.03–3.48] p=0.04). PNI markers (albumin, total lymphocyte count) could be seen as markers of inflammation rather than nutrition. There is a suggested relationship between very low body mass index (BMI) (<18kg/m2) and clinical outcomes.

No tool was identified as appropriate to screen for malnutrition, as distinct from inflammatory causes of weight-loss. Risk of cancer-cachexia and sarcopenia in older adults with cancer limits the tools analysed. Measures of food intake predicted mortality and should be included in clinical enquiry. A screening tool that distinguishes between malnutrition, cachexia, and sarcopenia in older adults with cancer is needed.

4.2.1 Abbreviations

Alb (Albumin), BAPEN (British Association for Parenteral and Enteral Nutrition), BMI (Body Mass Index), CASP (Critical Appraisal Skills Program), CC (Calf Circumference), CONUT (Controlling Nutritional Status), CRP (C-reactive Protein), ESPEN (European Society for Clinical Nutrition and Metabolism), GNRI (Geriatric Nutritional Risk Index), Hb (Haemoglobin), MAC (Mid-Arm Circumference), MUST (Malnutrition Universal Screening Tool), NSCLC (Non-Small Cell Lung Cancer), NRI (Nutrition Risk Index), OS (Overall Survival), POD (Post Operative Delirium), PNI (Prognostic Nutritional Index), SNAQ (Short Nutritional Assessment Questionnaire) 3-MinNS (3 Minute Nutrition Screening)

4.3 Introduction

Older adults with cancer are a growing population who require complex, multi-layered care to achieve the best possible clinical outcomes from anticancer treatment (329). One important, but often overlooked, aspect of this is nutritional care, which has been consistently shown to be one of the most predictive and treatable components of comprehensive oncogeriatric assessment (330).

Malnutrition is caused by a lack of intake or uptake of nutrition (133, 136), and risk screening is recommended (136) for all inpatients on admission and outpatients at their first appointment (14). A number of malnutrition screening tools exist (18, 331), although the most appropriate tool for identifying malnutrition in older adults with cancer is unknown. The varying diagnostic criteria for malnutrition between screening tools is reflected in the varying prevalence estimates; for example, the prevalence of malnutrition in older adults with gastrointestinal cancer varies between 20-52%, depending on the screening tool (15).

Malnutrition screening tools have often been validated against the Subjective Global Assessment (SGA) (332). The SGA was initially validated for use in end-stage renal disease (143), but has recently been shown to be less reliable than other nutritional screening tools to predict clinical outcomes in certain populations (333), such as the NRS-2002 screening tool which possesses higher specificity and positive predictive value for post-operative complications (334), and mortality (335) in hospitalised patients.

As well as varying markers, the marker thresholds used to determine nutritional risk differ between tools. For example, with regard to weight loss, the British Association for Parenteral and Enteral Nutrition (BAPEN) screening tool uses *any* unintentional weight loss (336); the Short Nutritional Assessment Questionnaire (SNAQ) uses >3kg in 1 month or >6kg in 6 months (337); the 3 Minute Nutrition Screening (3-MinNS) uses >7kg in an unspecified time frame (178); and the European Society for Clinical Nutrition and Metabolism (ESPEN) screening tool uses >10% in an unspecified time frame (142). Older adults with cancer exhibit further complexity given their higher risk of other weight-losing conditions, including sarcopenia and cachexia due to cancer or other co-morbidities. Cachexia, sarcopenia, and malnutrition have similar clinical presentations and diagnostic criteria (17, 19). However, malnutrition has a specific focus on the 'intake and utilisation' of nutrition, therefore a screening tool that can also identify problems with oral intake is required.

To establish which screening tool is most appropriate to identify malnutrition in older adults with cancer, markers of malnutrition and their thresholds must be investigated in relation to their ability to predict poorer clinical outcomes.

The objective of this systematic review is to identify, synthesise, and critically appraise the published evidence about markers of nutritional status in the older cancer patient. The findings will inform the most appropriate nutritional screening tool to use in this population.

4.4 Methods

The study protocol was registered with PROSPERO (221), and the review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (338).

4.4.1 Literature search

Searches were performed by AB and SG between the 6th and 8th December 2018, from database inception to search date in; Ovid® MEDLINE (Ovid MEDLINE®) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to December 5th 2018), EMBASE via OVID 1980 to 2018 Week 49, Web of Science Core Collection 1970 to search date, CINAHL Complete (Cumulative index to Nursing and Allied Health Literature) via EBSCO 1937 to search date, British Nursing Database via ProQuest 1994 to search date, and The Cochrane Database of Systematic Reviews and Cochrane Register of Controlled Trials (CENTRAL). No limits on publication date or language were applied.

An initial search combining keywords related to malnutrition, cancer, and older adults, using MeSH and text terms was conducted. On review of the findings, an additional supplementary search was conducted to include text terms for individual screening tools that were previously identified. See **Appendix 5** for the final MEDLINE search strategy. Forward and backward citation searching of all included studies, and relevant systematic reviews (8, 339, 340), was completed: we examined the reference lists of included studies and identified articles citing included studies in Web of Science.

4.4.2 Inclusion and exclusion criteria

Eligible studies had participants aged 70 years or older with any cancer diagnosis. Studies investigating markers of nutritional status, used in nutritional screening tools or objective nutritional indexes (18, 331), against any patient related outcome were included. All observational studies were included, and randomised control trials (RCTs) were included if study interventions were not nutrition related (e.g. nutritional interventions). Editorials, case studies, case reports and conference abstracts without subsequent full text publication were excluded along with review articles. Nutritional markers used in screening tools such as disease state and functional performance were excluded as all participants had cancer diagnoses. The relationship between functional performance and patient outcomes is an established individual risk factor for poor patient outcomes (341).

4.4.3 Study selection

All titles and abstracts retrieved by electronic searching were downloaded to an Endnote X8 library and duplicates were removed according to a published protocol (342). The remaining records were uploaded to the online citation-screening tool Abstrackr (343). Studies were initially dual screened independently (by AB and SG) on the basis of title and abstract against the eligibility criteria. Where one or more of the investigators were uncertain whether the article met the inclusion criteria, the abstract was included and the full-text article was included for review. All potentially relevant studies were retrieved and full-texts were reviewed by AB and SG, with any unresolved disagreements resolved by consensus or adjudication by a third reviewer (MJ).

Data were extracted by AB, using a custom data extraction form (221). Data extraction was piloted, reviewed and modified before a final extraction from the main papers of the included studies, with use of supplementary materials as necessary.

4.4.4 Risk of bias; quality appraisal

Each study was evaluated using the Critical Appraisal Skills Program (CASP) checklist (237) items 1 to 10. The cohort study checklist was used for all study designs. All included papers were evaluated by AB with a random 25% independently reviewed by GM. See **Figure 4** for quality assessment of studies.

4.4.5 Analysis

A narrative summary with descriptions and comparisons was completed. Meta-analyses were conducted with sufficient study data (*n* = ≥3 studies) with homogeneity of proxy marker thresholds and patient outcomes. Review Manager 5.3 (344) was used to conduct meta-analyses. The I^2 statistic was used to assess heterogeneity, with a random-effects model chosen if significant heterogeneity was indicated (345). Results were considered significant if confidence intervals did not include the null value, with corresponding significance values of $p<0.05$.

Figure 4: quality assessment of studies

STUDY NO. / QUESTION NO.	1	2	3	4	5A	5B	6A	6B	7	8	9	10		COMMENTS
AALDRICKS 2013	●	●	x	●	x	●	●	●	●	●	●	●	8.5	risk of selection bias
ALDRICKS 2015	●	●	●	●	●	●	●	x	●	●	●	●	9.5	
AALDRICKS 2016	●	x	x	●	●	●	x	●	●	x	●	●	6.5	missing data, univariate analysis ignored
APARICO 2013	●	x	x	●	x	●	x	●	●	●	●	●	7	missing data, recruitment
BAITAR, 2018	●	x	x	●	●	●	x	●	●	●	●	●	7.5	recruitment, risk of bias
BOURDEL-MACHASSON, 2016	●	x	x	x	●	●	x	●	●	●	x	●	5.5	recruitment, risk of bias, loss to follow-up n=33
CHAFOUR-ANDRE, 2011	●	●	●	●	x	x	x	●	x	●	x	●	6.5	risk of confounding
EXTERMANN, 2012	●	●	x	x	x	●	x	●	●	x	●	●	6	risk of bias, lack of results presented
FALANDRY, 2013	●	x	x	●	x	x	x	●	x	x	●	●	4.5	recruitment, risk of bias, missing data, data presentation
FIORELLI, 2014	●	x	x	x	●	●	●	●	x	x	x	x	3	recruitment, risk of bias, errors in data, data presentation
GIRRE, 2008	●	●	x	x	x	x	x	●	x	x	x	●	3.5	risk of bias, risk of confounding, missing data, data presentation
HARIMOTO, 2016	●	●	x	x	x	●	x	●	●	●	x	●	6	risk of bias
HOPPE, 2013	●	x	●	●	x	●	x	x	●	x	●	●	6.5	recruitment, missing data, inappropriate follow up time
HSU, 2015	x	x	●	x	x	x	●	●	x	x	x	x	2	unclear aim, risk of biases, risk of confounding, data presentation, inappropriate conclusions
KAIBORI, 2016	●	●	●	x	●	●	x	●	●	●	x	●	7.5	risk of selection bias
KANESVARAN, 2011	●	●	●	●	●	●	●	●	●	●	x	●	9	risk of bias
KIM, 2013	●	●	x	●	x	●	x	●	●	●	●	●	8	missing data
KIM, 2018	●	x	x	●	x	●	●	●	●	●	●	●	7.5	risk of bias
KUSHIYAMA, 2018	●	●	●	●	●	●	●	●	●	●	●	●	9	unknown follow-up or missing data
LAI, 2016	●	x	x	x	x	●	x	●	●	●	●	●	5.5	recruitment, risk of bias

LU, 2017	●	●	●	●	●	●	x	●	●	●	●	●	9.5	
MARENCO, 2008	●	x	●	x	●	●	x	●	●	●	x	●	6.5	selection bias
MIKAMI, 2018	●	x	x	●	x	●	●	●	●	x	x	●	5.5	recruitment, risk of bias, data presentation
MOSK, 2018	●	●	●	●	●	●	x	●	●	●	●	●	9.5	
NEUMAN, 2013	●	●	x	●	●	●	x	●	●	●	x	●	7.5	risk of bias in data collection
RAJASKARAN, 2016	●	●	●	●	x	●	x	x	●	●	x	●	7.5	risk of confounding
SAKURAI, 2016	●	x	●	●	●	●	●	●	●	●	●	●	9	recruitment
SAKURAI, 2019	●	●	x	●	●	●	x	●	●	●	x	●	7.5	missing data, risk of bias
SEKIGUCHI, 2017	●	●	x	●	x	●	●	●	●	x	x	●	6.5	risk of bias, data presentation, confounding
SHOJI, 2018	●	●	●	●	x	●	●	x	●	x	●	●	8	confounding, risk of bias
STANGL-KREMSER,2019	●	●	x	●	x	x	x	x	x	x	x	x	3	risk of bias, confounding, data presentation, missing data, inappropriate conclusion
TAKAMAI, 2015	●	x	x	x	●	●	●	●	●	x	x	x	4	recruitment, risk of bias, data presentation
TEI, 2010	●	x	x	●	●	●	●	●	●	●	x	●	7	recruitment, risk of bias
TEI, 2016	●	●	x	●	●	●	●	●	●	●	x	●	8	risk of bias, selection bias
TOMINGA, 2016	●	●	x	x	x	x	●	●	x	x	x	x	3	risk of bias, confounding, data presentation, missing information
TOYA, 2018	●	●	x	●	●	●	●	●	●	●	x	●	8	risk of bias
UENO, 2017	●	x	x	●	●	●	x	●	●	●	x	●	6.5	risk of bias, missing data
WATANABE, 2012	●	●	x	●	●	●	●	●	●	●	●	●	9	risk of bias in data collection
WATANABE, 2018	●	●	●	●	●	●	●	●	●	●	x	●	9	excluded missing data
YOSHIMATSU, 20116	●	x	x	x	x	x	●	●	x	x	x	x	2	recruitment, risk of bias, confounding, data presentation, selection bias
ZAUDERER, 2012	●	x	x	x	x	x	●	x	x	x	x	x	1.5	risk of bias, confounding, data presentation
ZHOU, 2018	●	●	x	●	●	●	●	●	●	●	x	●	8	risk of bias, missing data

4.5 Results

The search returned 5,997 unique articles after deduplication. Following screenings of titles and abstracts, n=703 full-text articles were assessed for eligibility, due to the need to examine demographic tables for age. From this, 42 studies, representing 21,032 participants, published between 2008 and 2019 were eligible for inclusion. (See **Figure 5**, PRISMA flow chart).

Table 15 provides a summary description of the included studies. There were 14 prospective (346-359), 24 retrospective cohort studies (360-383), 2 cross-sectional studies (384, 385) and 2 RCTs (386, 387). Sample sizes ranged from 24 (354) to 12,979 (367). Studies were globally represented; 24 studies from Asia (355-358, 361-363, 365, 368-371, 373-381, 383, 385), 14 from Europe (346-351, 353, 359, 360, 366, 372, 384, 386, 387), and five from North America (352, 354, 364, 367, 382).

Participants (46% men) with a number of cancer primary sites were represented. Twenty nine studies investigated single cancer primary sites: 10 gastric (358, 363, 365, 368-370, 373, 377-379), eight colorectal (364, 366, 367, 374-376, 381, 386), five non-small cell lung (NSCLC) (360, 362, 371, 380, 382), two hepatic (355, 361), and one each of breast, bladder, oesophageal and ovarian (346, 372, 383, 387) cancers. The remaining 13 studies investigated mixed cancer diagnoses (347-354, 356, 357, 359, 384, 385). All studies were based in secondary and tertiary healthcare settings; outpatient clinics; chemotherapy or radiotherapy treatments; or inpatients.

Figure 5: PRISMA 2009 flow diagram

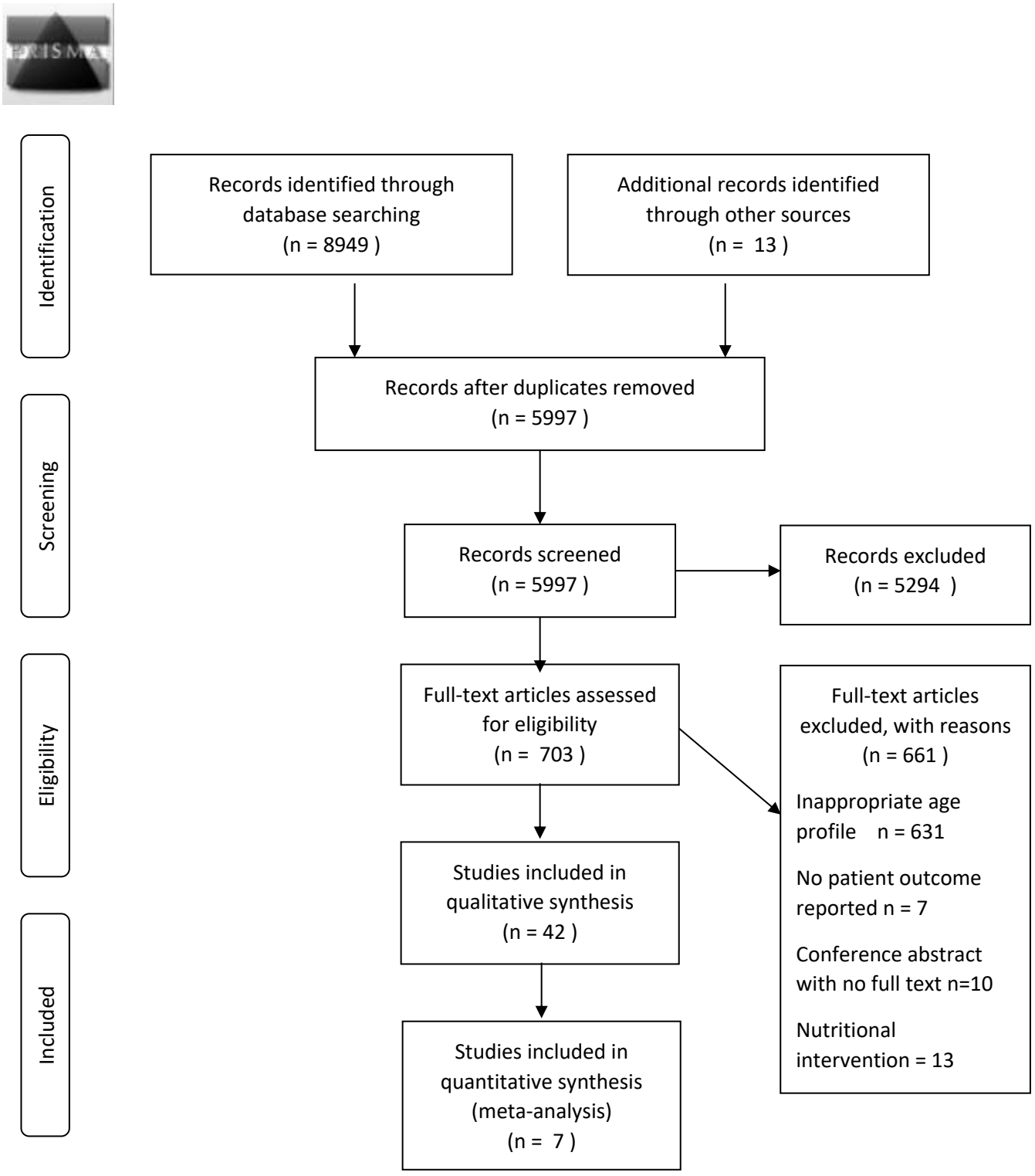


Table 15: Characteristics of included studies

Prospective Cohort Studies	Age, years	Sample Size, Gender	Cancer Diagnoses and Treatment	Malnutrition Proxy Marker(s) and units	Patient Outcome(s)	Follow up	Study results [95% CI]	Quality Score
Aaldricks, 2013 The Netherlands (346)	≥70 YO Mean 76 ± 4.8 Range 70 – 88	n=55 F=53 M=2	Advanced breast cancer. Chemotherapy.	Alb (</≥ 35g/l) Hb (</≥7.5mmol/l)	Overall mortality	Median 16 ± 13.7 months	No association between proxy markers and outcomes.	8.5 / 10 Risk of selection bias.
					≥4 Vs <4 cycles of chemotherapy	Median 11 months Range 0 – 57.		
Aaldricks, 2015 The Netherlands (347)	≥70 YO Mean 77	n=44 F=25 M=19	Non-Hodgkin's Lymphoma; diffuse large-β cell lymphoma and follicular lymphoma grade III. R-CHOP treatment.	Alb (</≥35g/l). Hb (6.8mmol/l).	Completion of chemotherapy. Mortality.	Median 46 months (0 – 101).	Hb associated with early treatment withdrawal: multivariate OR 5.41 [0.99 – 29.8] p=0.05 and mortality: HR 4.90 [1.76 – 13.7], p=0.0002.	9.5 / 10
Aaldricks, 2016 The Netherlands (348)	≥70 YO Median 75 Range 70 – 92	n=494 F=248 M=246	Various cancer diagnoses. Chemotherapy.	Declining food intake 3/12 (severe or moderate decrease / no decrease). Weight loss 3/12.	Feasibility of Chemotherapy ≥4 Vs <4 cycles	Median 17 months Range 1 – 101.	Declining food intake OR 2.00 [1.34 – 3.00], weight loss 3/12 OR 1.88 [1.26 – 2.80] associated with feasibility of chemotherapy in univariate analysis.	7.0 / 10 Missing data, unclear recruitment.

				Declining food intake 3/12 Reduced fluid intake (≤3 / 3-5 / ≥5 cups per day). Unintentional weight loss (3kg in 1/12 or 6kg in 2/12).	Overall mortality		Declining food intake, fluid intake ≤5 cups/day OR 1.76 [1.23 – 2.52] and weight loss 6/12 OR 1.38 [1.13 – 1.69] associated with mortality in univariate analysis.	
Baitar, 2018 Belgium (349)	≥70 YO Median 77 Range 70 – 95	n=328 F=194 M=134	Breast (38.4%, Colorectal 35.4%, Lung 15.5%, Prostate 6.4%, Ovarian 4.3%). 63.7% new diagnosis, 36.3% progression or recurrence. Surgery, chemotherapy, radiotherapy hormonal therapy.	Hb (</≥11.8 / 12g/dl)* Alb </≥ 35 / 37g/l)* CRP </>5 / ≥5mg/l* Markers also analysed as continuous variables	Overall survival	Median 60.3 months [95% CI: 58.6 – 62.6].	Hb, CRP and Alb associated with outcome as dichotomous variables: Hb HR 1.51 [1.16 – 1.96]. Alb HR 2.91 [1.44 – 2.52]. CRP: HR 1.82 [1.37-2.43]. CRP associated with outcome as continuous variable: HR 1.08 [1.06 – 1.11].	7.5 / 10 Unclear recruitment method.
Bourdel-Marchasson, 2016 France (350)	≥70 YO	n=606 F=287 M=319	Lung, Colon, Stomach, Pancreas, Ovary, Bladder, CUPSs, Biliary duct, Breast. Life expectancy ≥12 weeks. First line chemotherapy.	% Weight loss (none / <5%, 5 – 10%, >10%, missing). Decreased food intake 3/12 (severe / moderate / no decrease). Actual weight loss 3/12 (>3kg, 1 – 3kg / unknown / none). BMI (<19 / >19 – <21 / >21 – <23 / >23kg/m2)	1 year mortality	12 months.	In univariate analysis; reduced food intake 3.12, weight loss >3kg or unknown weight loss, BMI <23, number of full meals per day, <2 servings fruit and vegetables/day, self-fed with some difficulty, self-view of nutritional status, mid-arm circumference <21cm, calf	5.5 / 10 n=33 lost to follow-up, unclear recruitment method, risk of bias in data collection.

				Daily full meals (1 / 2 / 3 meals). Protein-rich foods (low / intermediate / high). Fruit & vegetable intake (<2 / ≥2 servings/day). Fluid intake (<3 / 3 – 5 / >5 cups/day). Self-view of nutritional status (malnourished / uncertain / no problem). Mode of feeding (assistance / self-fed with difficulty / no problem). MAC (<21 / <21 – <22 / >22cm). Calf circumference (<31 / >31cm).			circumference <31cm associated with outcome.	
Chaufour-André, 2011 France (351)	≥70 YO	n=71 F=33 M=38	Digestive, Upper aero- digestive, Gynaecological, Lung, Sarcomas, Other. Surgery for neoplastic pathology.	NRI </> 97.5. Unintentional weight loss.	Major complications. Infectious complications. Post-operative confusion.	1 month post-discharge.	Univariate analysis; NRI associated with post-operative complications: OR 0.79 [0.66-0.95]. No risk factors for postoperative complications could be identified.	6.5 / 10 Confounding not accounted for, risk of bias in recruitment.
Extermann, 2012 USA (352)	≥70 YO Median 75.5 Range 70 – 92	n=518 F=261 M=257	Lung, Breast, Non-Hodgkin's Lymphoma, Colorectal, Bladder, other. Chemotherapy.	BMI >25kg/m2. Hb (g/dl). Alb (g/dl).	Chemotherapy toxicity; grade 4 haematological or grade 3/4 non-haematological.	6 months.	No association between proxy markers and outcome.	6.0 / 10 Risk of bias recording proxy markers and outcomes.

Hoppe, 2013 France (353)	≥70 YO Median 77.4 Range 70 – 93	n=299 F=122 M=177	Colon, Pancreatic, Stomach, Ovarian, Bladder, Prostate, Lung, Non-Hodgkin's lymphoma, CUPs. First-line chemotherapy.	Weight loss (</≥ 10%). BMI (<19 / 19 – 23 / ≥23kg/m2). Alb (</≥ 35g/l). CRP (</≥ 5mg/l).	Functional decline (ADL score).	After first cycle of chemotherapy	Weight loss associated with functional decline in univariate analysis OR 1.86 [no CIs] p=0.05. No multivariate analysis given.	6.5 / 10 Risk of bias in recruitment, inappropriate follow up time.
Hsu, 2015 Canada (354)	≥70 YO Median 74.5 Range 70 – 84	n=24 F=7 M=17	Colorectal or Thoracic cancer. Chemotherapy.	Hand-grip strength (bottom 20th percentile)	Chemotherapy toxicity (grade 3 – 5). Dose reduction or delay due to chemotherapy toxicity. Discontinuation of chemotherapy due to toxicity. Hospitalization or ED visit due to chemotherapy.	12 months.	p-values only, no association between proxy marker and outcomes.	2.0 / 10 Risk of confounding, unclear recruitment, inappropriate conclusions.
Kaibori, 2016 Japan (355)	≥70 YO Median 77 Mean 78.2 ± 4.8 Range 70 – 89	n=71 F=19 M=52	Hepatocellular carcinoma. Hepatic resection.	BMI (</≥ 22kg/m2). Alb (</≥4g/dl).	Post-operative complications (Clavien-Dindo grade 2 – 4b)	Length of hospital stay: 13 days (6-189).	Alb associated with outcome in univariate analysis OR 3.66 [1.14 – 1.76], p=0.00292.	7.5 / 10 Risk of selection bias in recruitment and inclusion criteria.
Kanesvaran, 2011 Singapore (356)	≥70 YO Median 77 Range 70 – 94	n=249 F=96 M=153	All cancer diagnoses; Lung, Colorectal and Genitourinary 83.5%	BMI (</≥ 30kg/m2). Hb (</≥ 12g/dl). Alb (</≥35g/l).	Survival (median months)	No info.	Hb and albumin associated with outcome in univariate analysis. Multivariate analysis for Hb not given.	9.0 / 10 Missing data.

Kim, 2018 South Korea (357)	≥70 YO	n=301 F=93 M=208	Colorectal, Lung, Hepato-biliary, Stomach, Other. Stage III, IV or unknown. First-line chemotherapy.	Daily fluid intake (</> 3 cups per day).	≥Grade 3 chemotherapy toxicity	Post-chemotherapy cycles (range 25-75% 2-7 cycles).	Daily fluid intake associated with outcome.	7.5 / 10 Recruitment method not described.
Lu, 2017 China (358)	≥80 YO Range 80 – 93	n=165 F=30 M=132	Gastric cancer. Surgical resection.	PNI </≥45.	Systematic complications. Local complications. Overall survival. Recurrence free survival. Cancer specific survival.	5 years.	PNI associated with recurrence-free survival	9.5 / 10
Marenco, 2008 Italy (359)	≥70 YO Median 78 Mean 78 ± 4.8	n=571 F=220 M=351	Colorectal, Gastro-intestinal, Renal, Bladder, Other.	BMI </≥21kg/m2	Treatment recommendation (active vs palliative care). Survival.	Up to 60 months.	BMI associated with outcome.	6.5 / 10 High risk of selection bias.
Retrospective Cohort Studies	**Age, years**	**Sample Size, Gender**	**Cancer Diagnoses and Treatment**	**Malnutrition Proxy Markers**	**Patient Outcomes**	**Follow up**	**Study results [95% CI]**	**Quality Score**
Fiorelli, 2014 Italy (360)	≥70 YO Median 75 Mean 74.9 ± 2.6 Range 71 – 93	n=117 F=23 M=94	Non-small cell lung cancer. Curative resection.	BMI (≤ / > 18.5kg/m2) Alb (≥35g/l) Weight loss (≥5% 3/12)	Major complications. Early death (<3/12 post procedure).	3 months.	BMI and albumin associated with major complications in univariate analysis.	3.0 / 10 Risk of selection / recruitment bias, risk of bias in data collection, statistics errors.

Harimoto, 2016 Japan (361)	≥70 YO	n=139 F=41 M=98	Hepatocellular carcinoma. Curative hepatic resection.	BMI (kg/m2). Alb (g/dl). CRP (mg/dl). PNI.	Overall survival. Disease-free survival.	No info.	Univariate analysis; CRP associated with disease-free survival: HR 1.35 [1.14 – 1.59].	6.0 / 10 Risk of bias in data collection.
Kim, 2013 South Korea (362)	≥70 YO Median 76 IQR 72 – 80	n=122 F=37 M=85	Primary non-small cell lung cancer, ≥ stage IIIB. Admitted to hospital.	BMI (<18kg/m2).	Survival	6.2 months (IQR: 2.5 – 15.3).	BMI associated with outcome.	8.0 / 10 Missing data. Risk of bias in data collection.
Kushiyama, 2018 Japan (363)	≥75 YO Mean 79.6 ± 3.8	n=348 F=118 M=230	Gastric cancer. Gastrectomy.	BMI (<22kg/m2). GNRI (<92).	Post-operative complications (Clavien-Dindo grade 2 – 4)	No info.	GNRI associated with outcome	9.0 / 10
Lai, 2016 Canada (364)	≥80YO Median 83 Range 80 – 92	n=60 F= 29 M=31	Metastatic colorectal cancer. Chemotherapy.	Hb </≥100g/l..	Chemotherapy dose reduction / omission or delay >1 week. Chemotherapy discontinuation due to toxicity. Hospitalization within 30 days of chemotherapy. Overall survival.	No info.	Hb associated with overall survival	5.5 / 10 Recruitment not discussed. Missing data.
Mikami, 2016 Japan (365)	≥70 YO	n=267 F=92 M=175	Primary gastric cancer. Curative gastrectomy.	BMI (kg/m2). Hb (g/dl). PNI </≥ 40.	Overall survival. Gastric cancer specific survival.	5 years.	BMI and PNI associated with overall survival.	5.5 / 10 Risk selection bias.
Mosk, 2018 The Netherlands (366)	≥70 YO Median 76 IQR: 73 – 80	n=251 F=110 M=141	Colorectal cancer. Elective surgery.	Low skeletal muscle mass (<35.17 females cm2/m2, <43.19cm2/m2 males). Low skeletal muscle density.	Post-operative delirium.	Length of hospital stay.	Low skeletal muscle mass associated with outcome.	9.5 / 10

Neuman, 2013 USA (367)	≥80 YO Mean 84.4 ±3.7	n=12979 F=7976 M=5003	Colon cancer. Surgical resection.	Weight loss.	90 day mortality. 1 year mortality.	1 year.	No association between proxy marker and outcomes.	7.5 / 10 Risk of bias in data collection.
Sakurai, 2016 Japan (368)	≥75 YO Mean 79 ± 3.4	n=147 F=52 M=95	Gastric cancer. Curative gastrectomy.	BMI </≥ 22kg/m2. PNI ≤/> 43.8.	Overall survival.	5 years.	PNI associated with outcome.	9.0 / 10 Recruitment method not discussed.
Sakurai, 2019 Japan (369)	≥75 YO Mean 79.2 ± 3.5	n=175 F=59 M=116	Gastric cancer, stage 1. Gastrectomy.	BMI (<22kg/m2). PNI (<45).	5 year overall survival.	5 years.	PNI associated with outcome.	7.5 / 10 Risk of bias handing missing data and data collection.
Sekiguchi, 2017 Japan (370)	≥85 YO Median 86 Range 85 - 93	n=108 F=26 M=82	Gastric cancer. Endoscopic submucosal dissection.	PNI </≥ 44.6. BMI </≥ 24.3 kg/m2.	Overall survival.	5 years.	PNI associated with outcome.	6.5 / 10 Risk of bias handing missing data, data presentation.
Shoji, 2018 Japan (371)	≥75 YO Median 78 Range 75 – 91	n=272 F=117 M=155	Primary lung cancer. Surgical resection.	Pre-operative BMI </≥18.5kg/m2 Pre-operative PNI ≤/> 49.6. Pre-operative CONUT </≥1. Pre-operative GNRI ≤/>98.	Post-operative comorbidities. Overall survival.	Median 51 months Range 0 – 132.	GNRI associated with outcome.	8.0 / 10 Risk of bias in data collection.
Stangl-Kremser, 2019 Austria (372)	≥70 YO Median 82 IQR 75 – 86	n=68 F=13 M=55	Urothelial carcinoma of the bladder. Transurethral resection.	PNI </≥45.2. CONUT. BMI kg/m2.	Overall survival. Cancer specific survival.	Median 12.5 months (IQR: 5.1 – 23.5).	PNI associated with overall survival.	3.0 / 10 Risk of confounding, missing data.

Takama, 2015 Japan (373)	≥75 YO	n=190 F=60 M=130	Gastric cancer. Gastrectomy.	Alb </≥3.5g/dl. PNI </≥40.	Complications (Clavien-Dindo Grade ≥2).	Mean 46 months.	PNI p=0.005 [no CI] and Alb p=0.019 [no CI] associated with complications in ages ≥85.	4.0 / 10 Recruitment method not discussed. Data presentation.
Tei, 2010 Japan (374)	≥71 YO	n=129 F=54 M=75	Colorectal cancer. Surgery.	PNI (comparison of means).	Post-operative delirium.	30 days post-surgery.	PNI associated with outcome.	7.0 / 10 Recruitment method not discussed.
Tei, 2016 Japan (375)	≥75 YO Median 79 Range 75 – 93	n=311 F=140 M=171	Colorectal cancer. Laparoscopic surgery.	PNI (comparison of means). Hb (10 g/dl).	Post-operative delirium.	30 days post-surgery.	No association between proxy markers and outcome.	8.0 / 10 Risk of selection bias and bias in data collection.
Tominaga, 2016 Japan (376)	≥70 YO	n=239 F=118 M=121	Colorectal cancer. Curative resection.	PNI. Body weight. BMI. Alb. Hb (10 – 13 / 13 – 16 / 16 – 18 / <10 / > 18 g/dl).	Post-operative complications (Clavien-Dindo grade 2 – 5).	Median 25.7 months (range 0.2 – 69.2).	PNI p=<0.05 [no CI] and Alb p=0.04 [no CI] associated with complications.	3.0 / 10 Risk of bias in data collection and data presentation. Missing data.
Toya, 2018 Japan (377)	≥75 YO Median 78 Range 75 – 88	n=87 F=22 M=65	Non-curative gastric cancer. Endoscopic submucosal dissection.	PNI </≥ 44.8. GNRI ≤/> 92.	Overall survival.	Median 6.7 years (range 0.1 – 14.8).	No association between proxy markers and outcome.	8.0 / 10 Risk of selection bias and data collection
Ueno, 2017 Japan (378)	≥75 YO Median Range 75 – 91	n=117 F=35 M=82	Gastric cancer. Curative surgery.	PNI </≥ 40.	Overall survival. Disease-specific survival.	Median 52.9 (range 1.0 – 117.5).	No association between proxy marker and outcomes.	6.5 / 10 Risk of bias in data collection, missing data.

Watanabe, 2012 Japan (379)	≥75 YO Median Range	n=99 F=23 M=76	Gastric cancer. Curative intent gastrectomy.	PNI </≥44.7.	Overall survival.	5 years.	Proxy marker associated with outcome.	9.0 / 10
Watanabe, 2018 Japan (380)	≥75 YO Median 79 Range 75 – 88	n=131 F=63 M=68	Primary lung cancer. Complete surgical resection.	PNI </≥ 45.	Overall survival.	5 years.	Proxy marker associated with outcome.	9.0 / 10 Risk of selection bias
Yoshimatsu, 2016 Japan (381)	≥80 YO Median 83 Range 80 – 90	n=76 F=40 M=36	Colorectal cancer. Curative resection.	PNI </≥40.	3 and 5 year survival.	Median 30 months.	No association between proxy markers and outcomes.	2.0 / 10 Risk of bias data collection, confounding, selection bias, data presentation.
Zauderer, 2013 USA (382)	≥70 YO Median 75 Range 70 – 92	n=70 F=20 M=50	Metastatic non-small cell lung cancer. Chemotherapy.	Unintentional weight loss (Y/N). Alb </≥3.5g/dl. Anaemia (Y/N).	Chemotherapy complications; grade 3/4 hematologic and grade 4 non-hematologic toxicity. Treatment delay. Dose reduction. Hospitalization. Discontinuation of chemotherapy due to toxicity.	No info.	No association between proxy markers and outcomes.	1.5 / 10 Confounding not accounted for. Convenience sample. Risk of bias in data collection. Data presentation.
Zhou, 2018 China (383)	≥70 YO Median 79 Range 75 – 91	n=164 F=67 M=97	Oesophageal cancer. Radiotherapy ± chemotherapy.	NRI </≥100.	2 year overall survival. 2 year local-regional failure-free survival. 2 year distance metastasis-free survival.	2 years.	Proxy marker associated with outcomes.	8.0 / 10 Risk of bias in data collection. Missing data.

Cross-sectional Studies	**Age, years**	**Sample Size, Gender**	**Cancer Diagnoses and Treatment**	**Malnutrition Proxy Markers**	**Patient Outcomes**	**Follow up**	**Study results [95% CI]**	**Quality Score**
Girre, 2008 France (384)	≥70 YO Median 79 Range 70 – 97	n=105 F=87 M=18	Breast, Lung, Colorectal, Cervix, Endometrial, Ovarian, Prostate, Melanoma, Haematological. Other.	BMI (</≥ 23kg/m2). Hb (</≥ 12g/dl). Alb (20 – 35 / >35g/l).	Treatment plan modification.	NA	BMI associated with outcome, p=0.029 [no CI].	3.5 / 10 Risk of bias in data collection, selection bias, Data presentation.
Rajasekaran, 2016 Singapore (385)	≥70 YO Median 77 Range 70 – 94	n=244 F=95 M=149	Gastrointestinal, Lung, Genitourinary, Other.	BMI (</≥27.5kg/m2). Hb (</≥ 12g/dl). Dominant handgrip (per kg increase).	Caregiver burden.	NA	Hb associated with outcome	7.5 / 10 Risk of confounding, study design.
Randomized Controlled Trials	**Age, years**	**Sample Size, Gender**	**Cancer Diagnoses and Treatment**	**Malnutrition Proxy Markers**	**Patient Outcomes**	**Follow up**	**Study results [95% CI]**	**Quality Score**
Aparicio 2013 France (386)	≥75 YO Mean 80 ± 3.7	n=123 F=57 M=66	Metastatic colorectal cancer. Chemotherapy.	BMI (≤20 / 20 – 30 / ≥30kg/m2 Hb (</≥ 10 g/dl females, </≥ 11g/dl males)	Dose intensity reduction ≥33%. Grade 3 to 4 toxicity. ≥1 Hospitalization.	4 months after start of treatment.	No association between proxy markers and outcomes.	7.0 / 10 Risk of selection bias.
Falandry, 2013 France (387)	≥70 YO Median 79 Range 70 – 93	n=98 F=98 M=0	Epithelial FIGO stage III or IV ovarian cancer. Chemotherapy.	Alb </≥ 35g/l. BMI </≥21kg/m2.	Overall survival.	Median 17.4 months.	Alb associated with outcome in univariate analysis; HR 2.36, [no CI] p=0.003.	4.5 / 10 Risk of confounding, risk of bias in data collection.

4.5.1 Markers of nutritional status

Data extraction revealed 15 markers of nutritional status: four 'objective indexes' (Prognostic Nutritional Index [PNI], Controlling Nutritional Status Score [CONUT], Nutritional Risk Index [NRI], Geriatric Nutritional Risk Index [GNRI]; (351, 358, 361, 363, 365, 368-381, 383) see **Table 16**, six anthropometric markers (body mass index [BMI], weight loss, mid-arm and calf circumference; (348, 350, 352, 353, 355, 356, 359-363, 365, 367-372, 376, 382, 384-387); two measures of muscle strength (hand-grip, lean skeletal muscle mass by computed tomography [CT]; (354, 366, 385), three biochemical markers (haemoglobin, albumin and C-reactive protein; (346, 347, 349, 352, 353, 355, 356, 360, 361, 364, 365, 373, 375, 376, 382, 384-387); and food and fluid measures (348, 350, 357). Patient outcomes included survival, mortality, chemotherapy complications (including dose-reductions and toxicities), post-operative complications (including post-operative delirium [POD], functional decline and treatment modifications) and caregiver burden.

Table 16: Objective indexes

PNI (331)	PNI = 10 x albumin (g/dl) + 0.005 x total lymphocyte count (per mm3)
CONUT (388)	Serum Albumin (g/dl): ≥3.50 score 0, 3.00 – 3.49 score 2, 2.50 – 2.99 score 4, <2.50 score 6 Total lymphocyte count (mm3): ≥1600 score 0, 1200 – 1599 score 1, 800 – 1199 score 2, <800 score 3 Total cholesterol (mg/dl): ≥180 score 0, 140 – 179 score 1, 100 – 139 score 2, <100 score 3 CONUT = serum albumin score + total lymphocyte score + total cholesterol score
NRI (389)	NRI = (1.519 x serum albumin (g/dl)) + (41.7 x current weight (kg) / ideal body weight (kg))
GNRI (390)	GNRI = (1.489 x albumin (g/l)) + (41.7 x [weight / weight loss])

Key: PNI = Prognostic Nutritional Index, CONUT = Controlling Nutritional Status Score, NRI = Nutritional Risk Index, GNRI = Geriatric Nutritional Risk Index

4.5.2 Dietary intake

Two studies (348, 350) investigated five markers of food intake: declining (348) or decreasing food intake, number of daily full meals, protein-rich food intake, fruit and vegetable intake and mode of feeding (350). Only one study (348) performed multivariate analysis, observing 'declining food intake' to be associated with overall mortality. All other markers of food intake reported associations between patient mortality and declining food intake, regardless of the threshold or marker used for food intake. Two studies (348, 350) investigated three comparable scales of declining food intake at univariate level, allowing meta-analysis of results.

4.5.2.1 Meta-analysis

A random-effects model was used to combine odds ratios (ORs) for mortality, with meta-analysis suggesting that declining food intake is associated with worse increased risk of mortality in univariate analysis (OR 2.15 [95% CIs 1.61 to 2.86, *p*=<0.0001]), **Figure 6.**

Three studies (348, 350, 357) investigated the relationship between fluid intake and patient outcomes; finding an association in two studies between fluid intake <3 cups/day with chemotherapy toxicity in univariate analysis (357), and fluid intake <5 cups/day with overall mortality in univariate analysis (348). However, one study observed no relationship between fluid intake and mortality (350).

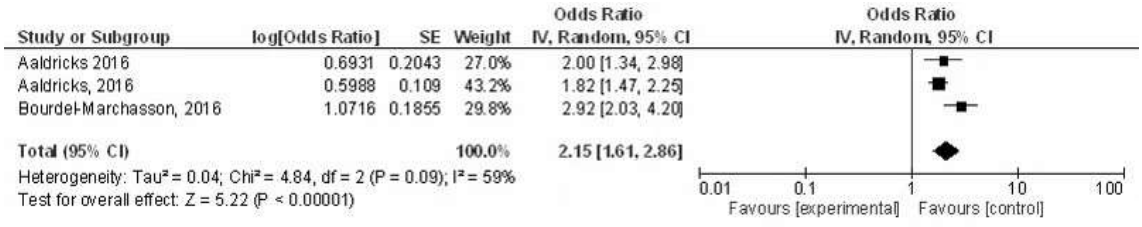


Figure 6: Forest plot assessing the correlation between declining food intake and mortality

Studies ordered by year (SE: standard error, IV: inverse variance, CI: confidence interval)

4.5.3 Objective indexes

Four objective indexes were identified in the search; PNI, CONUT, NRI and GNRI, of which 17 studies investigated PNI (358, 361, 365, 368-381), three GNRI (363, 371, 377), two CONUT (371, 372) and two investigated NRI (351, 383). All but one study (383) investigated the use of objective indexes in surgical patients.

4.5.3.1 Prognostic nutritional index (PNI)

PNI was initially developed to assess pre-operative nutritional status to predict post-operative complications in patients undergoing gastrointestinal cancer surgery. PNI is calculated using serum albumin concentration and the peripheral blood lymphocyte count (331). Cut-off points of <40 and <45 were initially suggested to predict risk of surgical complications. Thirteen studies investigated the relationship between PNI and overall survival (OS); (358, 361, 365, 368-372, 377-381).

4.5.3.2 Meta-analysis

Due to the heterogeneity in PNI thresholds used, meta-analysis of only four studies, using receiver operating characteristic curve estimates for OS was possible. A random-effects model was used to combine hazard ratios (HRs) for OS and meta-analysis suggesting that lower Preoperative PNI is associated with worse OS (HR 1.89 [95% CI 1.03–3.48, p = 0.04]), Fig. 2, I2 = 65%. See **Figure 7**.

Two studies investigated PNI and risk of POD (374, 375), which demonstrated mixed results in multivariate analysis. Both a statistically significant association (OR 1.257 [1.039 – 1.413] *p*=0.003) (374) and no association (OR 1.016 [0.959 – 1.080] *p*=0.475) (375) with POD were found (375). Two studies investigated PNI to predict risk of post-operative complications, although this only met statistical significance in univariate analysis (373, 376).

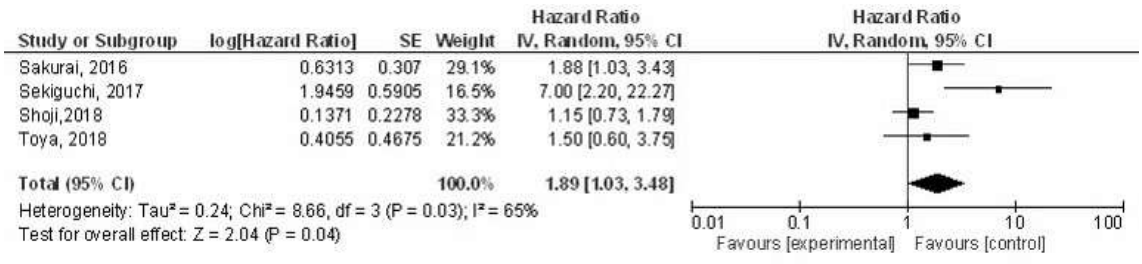


Figure 7: Forest plot assessing the correlation between Prognostic nutritional index and overall survival

Studies ordered by year (SE: standard error, IV: inverse variance, CI: confidence interval)

4.5.3.3 Geriatric nutritional risk index (GNRI)

Two studies (363, 371) found an association between GNRI and poorer patient outcomes. Low GNRI scores of <92 associated with post-operative complications Clavien-Dindo grade ≥2 (HR 2.02 CI: 1.13 – 3.66]) (363), and normal GNRI (≥98) associated with improved OS (HR 1.672 [CI: 1.079 – 2.581]) (371). A third study (377) observed no association between GNRI and OS (*p*=0.91). Thresholds for GNRI varied between 92 and 98.

4.5.3.4 Controlling nutritional status score (CONUT)

One study (371) reported an association between CONUT and OS in multivariate analysis, but no relationship with post-operative complications. A second smaller (*n* = 68) study (372) found no association between CONUT and OS or cancer-specific survival.

4.5.3.5 Nutritional risk index (NRI)

Two studies investigating NRI found low NRI was associated with worse patient outcomes (383) (351). One (383) investigated NRI as a predictor of outcomes after anticancer therapies in oesophageal cancer and found that NRI was associated with poorer 2-year OS and distant metastasis-free survival in multivariate analysis. The second (351) undertook a smaller study (n = 71) and found low NRI to be associated with post-operative complications in univariate analysis, but not with either major or infectious complications.

4.5.4 Anthropometric markers

Four anthropometric markers were identified in the reviewed articles; BMI, weight loss, mid-arm circumference (MAC) and calf circumference (CC), of which, 21 studies investigated BMI (350, 352, 353, 355, 356, 359-363, 365, 368-372, 376, 384-387), eight weight loss (348, 350, 351, 353, 360, 367, 376, 382) and one for MAC and CC (350).

4.5.4.1 Body mass index (BMI)

Due to variable BMI thresholds and patient outcomes, meta-analysis of results was not possible. Four studies (359, 360, 362, 365) conducted multivariate analysis of BMI on patient outcomes; with one (360) finding an association between BMI <18kg/m^2 and death within three months of surgery. Another found BMI <18kg/m^2 associated with shorter survival (362). Multivariate analysis also identified associations with BMI and OS (365) and the clinical decision of active *versus* palliative treatment (359).

In univariate analysis, associations were reported between a BMI of 19-23kg/m^2 and patient outcomes; of low BMI with mortality (350), treatment plan modification (384), post-operative complications (371) and OS (361). The remaining 13 studies (352, 353, 355, 356, 363, 368-370, 372, 376, 385-387) found no associations between BMI and patient outcomes. BMI thresholds were heterogeneous and ranged from 18kg/m^2 (362) to 30kg/m^2 (356).

Participants in the three studies (360, 362, 371) investigating BMI <18kg/m^2 on patient outcomes were all diagnosed with NSCLC. These studies observed associations between low BMI and poorer patient outcomes.

4.5.4.2 Weight loss

Only one study (360) conducted multivariate analysis of weight loss on patient outcomes. A 5% weight loss in 3 months was associated with post-operative early death within three months (360).

Three studies investigated the effect of weight loss on mortality. Two studies (348, 350) found an association between weight loss and mortality, where weight loss of between 5-10%, >10%, >3kg or unknown weight loss were associated with 1-year mortality (350). Weight loss in the past six months was also associated with mortality (348). The largest study, of 12,979 patients with colon cancer reported no association between 'weight loss' and 90-day or 1-year mortality rates (367). Three studies (351, 376, 382) investigating weight loss and treatment complications found no association.

Thresholds for weight loss varied from 5% (360), <5%, 5-10%, >10% (350), 1-3kg, >3kg (350), and unspecified weight loss (367) in three month (360), six month (351) or unspecified timeframes (382).

4.5.4.3 Mid arm circumference (MAC) and Calf circumference (CC)

Only one study investigated MAC and CC in relation to patient outcomes (391), finding CC <31cm and MAC <21cm to be associated with mortality in patients receiving chemotherapy in univariate analysis.

4.5.4.4 Muscle strength

Two measures of muscle strength were identified in the reviewed articles; hand-grip strength (354, 385) and lean skeletal muscle-mass by CT (366). A pilot study with 24 participants found no association between grip-strength and chemotherapy toxicity (354). Two studies reported associations between lean skeletal muscle mass with POD in multivariate analysis (366), and grip-strength with caregiver burden in univariate analysis (385).

4.5.5 Biomarkers

Three biomarkers were investigated; haemoglobin (Hb), albumin (Alb) and CRP, of which 12 studies investigated Hb (346, 347, 349, 352, 356, 364, 365, 375, 382, 384-386), 14 Alb (346, 347, 349, 352, 353, 355, 356, 360, 361, 373, 376, 382, 384, 387) and three CRP (349, 353, 361).

4.5.5.1 Haemoglobin

Five studies (346, 347, 349, 364, 365) conducted multivariate analysis of Hb on patient outcomes; with two studies (349, 364) finding associations with Hb and OS, and a third study

reporting no association (365). One small study (*n = 44)* (347) observed an association with Hb and mortality. No relationship between Hb and chemotherapy toxicity or complications were seen in three studies (352, 382, 386). However, associations were seen between Hb and survival (356), POD (375) and caregiver burden (385). Thresholds for Hb ranged between 100g/l (364) and 132g/l (349) and the presence or absence of 'anaemia' (382).

4.5.5.2 Albumin

Four studies (346, 347, 349, 360) conducted multivariate analysis of albumin to predict patient outcomes; with only one study (349) finding an association with OS, and one study with major post-operative complications (360). No association with mortality (346, 347), completion of chemotherapy (346, 347) or death within three months of surgery were found (360). Univariate associations between Alb and post-operative and chemotherapy-related complications were seen in four studies (355, 373, 376, 382), and OS in two (356, 387). There were no observed associations between Alb and OS or disease-free survival (361), functional decline (353), or chemotherapy toxicity (352) in three other studies. Thresholds of Alb varied between 35g/l (346) and 40g/l (355).

4.5.5.3 C-reactive protein

An association between increasing CRP and OS was seen in one study (349) through multivariate analysis. There were no observed relationships between CRP and OS (361) or functional decline (353).

4.6 Discussion

Forty-two papers, representing 21,032 participants, investigating the associations of 15 makers of nutritional status with patient outcomes, were identified for review. Our meta-analysis of three studies regarding declining food intake shows an association between reduced food intake and mortality, but does not assess utilisation. Our meta-analysis of four studies shows an association between poorer PNI scores and clinical outcomes, but this score measures inflammatory markers (which may indicate increased energy requirement) but does not assess poor oral intake. PNI alone, therefore cannot distinguish between cachexia and malnutrition.

Measures of dietary intake *and* utilisation are essential in diagnosing malnutrition, as these changes in consumption or assimilation can lead to net calorific deficit and consequent weight loss. Assessments of eating and drinking, despite being a direct measure of intake, are inadequately assessed in commonly used malnutrition screening tools (e.g. ESPEN criteria, MUST). Several screening tools included an assessment of appetite. Appetite may correlate with dietary intake in patients with cancer, although it is only a proxy marker of malnutrition; for example, a patient with dysphagia due to localised oesophageal cancer may be hungry but unable to eat. Food and fluid intake arguably have the greatest face and content validity for determining nutritional risk. From the available evidence, there appears to be some evidence that reduced food and fluid intake were associated with adverse patient outcomes in older adults with cancer, with meta-analyses suggesting an association between declining food intake with mortality, However, there is an urgent need for more evidence, and in particular studies which appropriately control for potential confounding variables via multivariable analyses.

Whilst proxy markers of malnutrition can be easily used and are commonly available, their value against direct anthropometric markers or measures of food and fluid intake is limited. See **Table 17***,* for comparison of malnutrition screening tool and objective indexes content, compared with malnutrition markers identified in this review.

PNI was devised in 1984 as a risk score relating post-operative complications with baseline nutrition, using albumin and lymphocyte counts (331). Our finding of an association between low PNI and worse OS is consistent with other recent meta-analyses of all adults with cancer undergoing surgery (392, 393) (394). Albumin and common laboratory tests for inflammation (e.g. CRP and white cell counts) are useful as predictors of prognosis in people with cancer e.g. Glasgow Prognostic Score (395). However, they are not specific to malnutrition and are not recognised as a diagnostic markers for malnutrition (150).

Table 17: Malnutrition screening tools and objective indexes compared with malnutrition markers identified in the review

	Biochemical			Anthropometrics					Dietary Intake	
	Hb	Alb	CRP	Weight loss	BMI	MAC / CC	Hand -grip	CT (LSMM)	Food	Fluid
BAPEN				●	●	●			●	
CNST				●					●	
CONUT		●								
ESPEN				●	●			●*		
GNRI		●		●						
INSYST				●					●	
MST				●					●	
MSTC				●	●				●	
MUST				●	●				●	
NRI		●		●						
NRS-2002				●	●				●	
NUFFE				●					●	●
PNI		●								
SGA				●					●	
SNAQ				●					●	
3-MinNS				●	●					

*Low fat free mass index used instead of low skeletal muscle mass, defined as <15 kg/m2 in females and <17 kg/m2 in males

Key: Alb (Albumin), BAPEN (British Association for Parenteral and Enteral Nutrition), BMI (Body Mass Index), CC (Calf Circumference), CNST (Canadian Nutrition Screening Tool), CONUT (Controlling Nutritional Status), CT (Computerized Tomography), CRP (C-reactive Protein), ESPEN (European Society for Clinical Nutrition and Metabolism), GNRI (Geriatric Nutritional Risk Index), Hb (Haemoglobin), INSYST (Imperial Nutrition Screening System), LSMM (Lean Skeletal Muscle Mass), MAC (Mid-Arm Circumference), MST (Malnutrition Screening Tool), NRS-2002 (Nutrition Risk Screening), MUST (Malnutrition Universal Screening Tool), NRI (Nutrition Risk Index), NUFFE (Nutritional Form for the Elderly), PNI (Prognostic Nutritional Index), SNAQ (Short Nutritional Assessment Questionnaire), SGA (Subjective Global Assessment), SNST (3-MinNS (3 Minute Nutrition Screening)

The single biomarkers identified in this review suggest no clear association with patient outcomes. Although reduced haemoglobin can be caused by dietary deficiency, it may also be a feature of inflammation, chronic disease, bone marrow suppression from anticancer treatments and other wasting diseases (e.g. cachexia and sarcopenia (22, 59)). Although the clinical presentation of malnutrition, cachexia and sarcopenia overlap, **Table 18***,* the management of each differs (19, 22, 59, 133). Therefore, the use of non-specific biochemical and clinical markers, or objective indices, which identify inflammation – albeit giving information about increased metabolic and therefore nutritional requirements – tell us nothing about dietary intake. Therefore, in the absence of information about dietary intake, they may reduce the specificity for malnutrition in an older population at high risk of all three conditions.

Four anthropometric markers were examined in this review: BMI, weight loss, MAC and CC. We found weight loss was associated with worse clinical outcomes in older adults with cancer. The varying thresholds in required percentage weight loss and the timeframes for weight loss used in the analysed literature, precluded meta-analysis or identification of an appropriate threshold for weight loss to indicate malnutrition in older adults with cancer. However, weight loss does have face validity as a marker of malnutrition. Weight loss is used in most malnutrition screening tools (18).

As with weight loss, varying thresholds prohibited meta-analysis of BMI. We found a low BMI ($<18 kg/m^2$) predicts poorer outcomes, particularly in lung cancer patients (360, 362, 371). MAC is known to correlate with BMI in hospital inpatients (396). BMI is a simple measure, easy to implement in clinical practice but does not differentiate between fat and muscle and repeat measures are needed to be clinically useful. Adiposity mass increases with age and muscle decreases without significant changes to BMI (397, 398), and the presence of sarcopenic obesity should be considered.

Table 18: Diagnostic criteria and definitions for cachexia, sarcopenia, and malnutrition

		Weight loss	BMI	Fat loss	Fat increase	Loss of muscle mass	Loss of muscle strength / function	Low FFMI	Adverse clinical outcome	Disease state	Age related	Catabolic / Imflam response	Abnormal Biomark	Anorexia	Insulin Resistance	Fatigue	Oral intake
Cachexia Diagnoses	Evans et al., 2008 (22)	▲ □		± □		□	▲	▲	□	▲ □		▲ □	▲	▲ □	□	▲	
	Fearon et al., 2011 (19) International Consensus	▲	▲	± □		▲ □	□					□					□
Sarcopenia Diagnoses	Muscaritoli et al., 2010 (23)					▲ □	▲ □										
	Fielding et al., 2011 (67) IWGS				± □	▲ □	▲ □			□*	□	□*			□*		□*
	Morley et al., 2011 (399) **$** International Consensus					□	□										
	Cruz-Jentoft et al., 2019 (17) **$** European Consensus					▲ □	▲** □		□								
Malnutrition Diagnoses	NICE, 2006 (138) **§**	▲	▲														
	White et al., 2012 (150) *** (ASPEN & AND Consensus)	▲ □		▲		▲	▲					± □					▲□
	Cederholm et al., 2015 (140) (ESPEN Consensus) **§**	▲	▲					▲									
	Cederholm et al., 2019 (145) GLIM Criteria **§** ****	▲	▲			▲				▲							▲
	Nutrition screening tools (18)	▲	▲	▲		▲	▲			▲	▲	▲	▲	▲		▲	▲

▲ Diagnostic criteria □ Definition ± with or without

*Causes of sarcopenia may include

** Presence of low muscle quantity/quality and low physical performance indicates severe sarcopenia

*** Definition adapted from Jensen et al., 2009 (183)

****Plus 'at risk' by one of: NRS-2002, MNA-SF, MUST, ESPEN, ASPEN/AND, SGA, Evans 2008, PEW 2008, Fearon 2011

Key: BMI = body mass index, FFMI = fat free muscle index, Inflam. = inflammation. Biomark. = Biomarker. NICE = National Institute of Health and Care Excellence. APSEN = American Society for Parenteral and Enteral Nutrition. AND = Academy of Nutrition and Dietetics. IWGS = International Working Group for Sarcopenia. PEW = Protein Energy Wasting in chronic kidney disease. NRS-2002 = Nutrition Risk Score 2002. MNA-SF = Mini Nutrition Assessment – Short Form. SGA = Subjective Global Assessment

4.6.1 Strengths and limitations

A strength of this study was the broad inclusion criteria of patients with any cancer diagnosis, markers of nutritional status and patient outcomes. This allowed a comprehensive analysis of potential markers of nutritional status, and appraisal of the evidence surrounding the validity of outcomes in older adults with cancer. We chose to focus on adults aged 70 years and over with cancer as this population is both growing and complex; we address an important clinical issue and identify a gap in clinical practice. This patient group may present with multimorbidity and co-existent cachexia and sarcopenia. Cancer patients are frequently neglected from clinical trials and surgical and pharmacological interventions require correction of nutritional deficits before treatment commences.

There are a number of limitations. Firstly, due to the heterogeneity in markers, marker thresholds, cancer diagnoses, treatment types and study quality, meta-analysis of most extracted data was not possible. Secondly, our aim was to study malnutrition, therefore the search strategy was not designed to capture all studies of general prognostic markers in older adults with cancer. Few studies included biomarkers. We acknowledge that some studies investigating Hb, Alb and CRP outside of a focus on malnutrition may have been missed for this population. However, we are unlikely to have missed any critical markers of malnutrition. Finally, although lower weighting was given to lower quality studies within results synthesis, due to the number of lower quality studies, results may be treated with caution.

4.6.2 Implications for clinical practice and research

Measures of dietary intake should be sought as part of routine nutritional assessment. The appropriateness of using 'proxy' markers of malnutrition should be reconsidered, especially those overlapping with inflammation in older adult patient groups with co-morbid conditions or acute illness. Further research is required into the appropriate thresholds for markers of nutritional status in this complex population. A screening tool that can identify and differentiate between malnutrition, cachexia, and sarcopenia in older adults with cancer, and which is usable in clinical practice, may allow targeted and appropriate treatment of these conditions. Currently, there is none that can assess all three conditions.

4.7 Conclusion

We could not identify a single tool suitable to screen for malnutrition risk in older adults with cancer. Markers of inflammation and measures or oral intake are used and are associated with clinical outcomes. However, alone, they cannot distinguish between risk of malnutrition, sarcopenia, and cachexia (which may co-exist in older adults with cancer). Dietary intake measures in conjunction with others, which measure nutritional utilisation, would be helpful. The value, and best way, of differentiating between malnutrition, cachexia, and sarcopenia for older adults with cancer remains unanswered.

4.8 Summary

This chapter presented the methods, results and discussion of a systematic review of the relationship between markers of malnutrition and clinical outcomes in older adults with cancer. From this review, no single screening tool could be identified as appropriate for assessing malnutrition in older adults with cancer. This review identified 15 markers of malnutrition in the published literature, with variable thresholds used to predict outcomes, of which the outcomes used were also variable. This review identified three markers of malnutrition with evidence of impact on patient outcomes, of; prognostic nutritional index, declining food intake, and very low body mass index, however, the appropriateness of 'proxy' markers on assessing nutritional status require consideration, particularly with the overlap of other nutrition-related wasting disorders with analogous diagnostic criteria.

In the next chapter, **Chapter Five**, a second systematic review, of patient, family and carers' experiences of nutritional screening, will be presented.

Chapter 5: Patient, family, and carer experience of nutritional screening: a systematic review

5.1 Chapter introduction

This chapter presents the text of an article published in the Journal of Nutrition and Dietetics in 2020. The text used for this chapter is identical to that in the published article, except for reference numbers, table and figure numbers and section numbers. Additionally, online supplementary material has been presented in the thesis appendices, with subsequent references to these being changed in the text in relation to this.

This review aimed to provide an overview of patients, their families, and carers' experiences and views of nutritional screening within the published literature. Due to the limited research regarding experiences of nutritional screening in older adults with cancer, this review included nutritional screening for all adults, regardless of disease status.

5.1.1 Author contributions

The idea for this research was conceived by myself, with support from my supervisor Miriam Johnson. I developed and conducted the search with specialist advice from Sarah Greenley. I performed data extraction for all papers, with 25% of data checked by PhD student Gordon McKenzie. I performed the data analysis, with themes discussed with PhD student Michael Patterson and Miriam Johnson. I wrote the manuscript. All authors read and approved the final published manuscript.

5.1.2 Article reference

Bullock, A.F., Greenley, S.G., Patterson, M.J., McKenzie, G.A.G., Johnson, M.J. (2020) Patient, family and carers experiences of nutritional screening: a systematic review. Journal of Human Nutrition and Dietetics. 34(3): pp.595-603

5.2 Abstract

Despite recommendations for nutritional risk screening of all inpatients, outpatients, and care home residents, and work to assess clinician's experiences and the validity of tools, little attention has been paid to the experiences of patients undergoing nutritional screening. This review aims to synthesise systematically the current evidence regarding patients, their families and carers experiences and views of nutritional risk screening.

A systematic search was performed in MEDLINE, Embase, PsychINFO, CINAHL, Web of Science and British Nursing Database (inception – July 2019); with screening terms related to malnutrition, screening tools and experience. Titles, abstracts, and full-text papers were independently reviewed by two reviewers, and quality-appraised. Qualitative papers and quantitative surveys were included. A narrative review of surveys and thematic framework synthesis of interviews were used to identify themes.

Nine studies, including five qualitative interview papers, were included. Qualitative and quantitative study results were combined using a matrix chart to allow comparison. Surveyed participants reported processes of nutritional screening as acceptable. Three key themes emerged from qualitative data: 1) experience of nutritional screening; 2) misunderstanding of malnutrition: causes, role of screening, and poor self-perception of risk, and 3) barriers to and opportunities for change.

Although the screening process is acceptable, patients' misunderstanding of, and poor knowledge regarding causes and consequences of malnutrition result in reduced risk perception and disbelief or disregard of nutritional screening results. Findings should inform policy and clinical practice, and highlight the known paucity of data regarding the effectiveness of screening on clinical outcomes.

5.2.1 Abbreviations

DETERMINE (DETERMINE Your Nutritional Health), HCP (Health Care Professional), INSYST I & II (Imperial Nutritional Screening System I & II), MNA (Mini Nutritional Assessment), MNA-SF (Mini Nutritional Assessment Short Form), MST (Malnutrition Screening Tool), MUST (Malnutrition Universal Screening Tool), NICE (National Institute for Health and Care Excellence), PG-SGA (Patient Generated Subjective Global Assessment), SCREEN II (Seniors in the Community – Risk Evaluation for Eating and Nutrition), YO (years old)

5.3 Introduction

Screening for the risk of malnutrition is recommended by the National Institute of Health and Care Excellence (NICE) in multiple clinical care settings, including the screening of all hospital inpatients on admission, hospital outpatients and in primary care surgeries, both at their first clinic appointment and upon clinical concern, and care homes residents upon clinical concern (138).

Given such extensive screening recommendations, validation of screening tools (400) their utility, ease of use by clinical staff, including time taken to complete screening and opinions on the methods have been conducted (401). However, less attention has been paid to the experiences and views of patients, their families and carers when reviewing the acceptability of the screening process. UK National Screening Committee guidance recommend that screening is simple, safe and acceptable to the target population (402). Although NICE recommend nutritional screening, they also highlight the lack of evidence regarding the benefit of screening, or most appropriate way to conduct screening (138).

Arguments in favour of nutritional screening include early detection and treatment of nutritional problems associated with negative patient outcomes (403). However, the impact and effectiveness of nutritional interventions to manage malnutrition, due to heterogeneous and low-quality studies, are unclear (184, 404). Therefore, burdens of screening must be considered alongside any potential benefits, as screening may increase anxiety and distress following a positive diagnosis (405).

This review aims to identify and summarise the available published evidence regarding patients', family, and carers' experiences of nutritional screening.

5.4 Methods

A systematic review of the literature, including data from both quantitative and qualitative texts, was conducted in accordance with the Cochrane Handbook for Systematic Review of Interventions (406). The study protocol was registered with the international prospective register of systematic reviews, PROSPERO (Registration No: CDR42019140859) (407). and is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (338).

5.4.1 Literature search

Searches were performed by AB and SG on 3rd July 2019 in the databases Ovid MEDLINE(R) ALL 1946 to July 02, 2019, Embase via OVID 1974 to 2019 Week 26, PsychINFO via OVID 1987 to June Week 4 2019, CINAHL Complete via EBSCO 1937 to 02 July 2019, ISI Web of Science: Science Citation Index Expanded 1970 to 03 July 2019, and British Nursing Database via ProQuest. The search was updated on the 5th June 2020. No limits on publication date or language were applied. The search combined database-specific indexed terms and textwords related to the two main concepts: Nutritional Assessment of malnutrition, or individual malnutrition screening tools, AND experience or potential harms of screening. See **Appendix 6** for the MEDLINE search strategy, which was translated to alternate databases as required. Forward and backward citation searching of all included studies was completed.

5.4.2 Inclusion and exclusion criteria

Eligible studies included participants aged 18 years or older, from any clinical setting with any diagnosis. Studies investigating patients', their families or informal carers' views or experiences nutritional screening were included. Qualitative and quantitative studies which included surveyed responses or questions regarding views of nutritional screening, were included. Studies which reviewed self-screening of nutritional status, focusing on 'ease of use', rather than experiences or opinions of screening were excluded. Case reports, editorials, opinion pieces, and papers reviewing nutritional screening for eating disorders, (e.g. anorexia nervosa), were excluded.

5.4.3 Study selection

All citations retrieved by electronic searching were downloaded to an Endnote X8 library, with duplicates removed according to published protocol (408). Remaining records were uploaded to Covidence systematic review software (409). Study titles and abstracts were independently screened (by AB and SG) against eligibility criteria. All potentially relevant studies were retrieved, with full texts reviewed by AB and SG. Disagreements were resolved by consensus or adjudication by a third reviewer (MJ). A custom data extraction form (407), was used, piloted,

reviewed, and modified before final data extraction of included studies was completed (by AB); a random 25% were independently extracted by GM.

5.4.4 Quality assessment

Each study was appraised using the Mixed Methods Appraisal Tool (MMAT) (410). All included papers were evaluated by AB with a random 25% independently reviewed by GM. Disagreements were resolved by consensus. See **Figure 8** for studies quality assessments.

5.4.5 Analysis

A narrative summary with descriptions and comparisons was completed for quantitative studies, providing an initial descriptive summary and explanation of characteristics of the included studies (411, 412). A narrative approach was used to analyse the relationship within and between studies, and assess the overall strength of the evidence (411). Qualitative results were reported in accordance with the Enhancing Transparency in Reporting the Synthesis of Qualitative research (ENTREQ) guidance (413). Thematic synthesis was used for the qualitative findings using Thomas and Harden methodology (414). Combining qualitative findings allowed new and generalisable knowledge to be generated. Synthesis was performed in three stages; i) initial coding of data regarding experiences of nutritional screening, (conducted by AB), ii) descriptive themes were generated, with codes grouped into categories (AB and MP), and iii) analytical themes generated both inductively and deductively, with authors (AB and MP) generating themes independently, then through discussion with a third author (MJ). Participants quotes and authors interpretations of responses were used within the qualitative synthesis. Results from qualitative and quantitative syntheses were combined and charted into a matrix to allow final comparison between studies, see **Appendix 7**. In view of the focussed nature of the synthesis, a theoretical framework was not used to underpin the analysis.

Figure 8: Study quality assessment

Mixed Methods Appraisal Tool (MMAT) Quality assessment

First author, year		**4. QUANTITATIVE DESCRIPTIVE STUDIES**					**1. QUALITATIVE STUDIES**				
		4.1. Is the sampling strategy relevant to address the research question?	4.2. Is the sample representative of the target population?	4.3. Are the measurements appropriate?	4.4. Is the risk of nonresponse bias low?	4.5. Is the statistical analysis appropriate to answer the research question?	1.1. Is the qualitative approach appropriate to answer the research question?	1.2. Are the qualitative data collection methods adequate to address the research question?	1.3. Are the findings adequately derived from the data?	1.4. Is the interpretation of results sufficiently substantiated by data?	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation ?
Callen	2004						Yes	Yes	Can't tell	No	Yes
Balstad	2019	Yes	Can’t tell	Yes	No	Yes					
Cawood	2012	Yes	Can't tell	Can't tell	No	Yes					
Cawood	2018	Yes	Can't tell	Yes	No	Yes					
Di Bella	2018	Yes	Can't tell	Yes	Yes	Yes					
Hamirudin	2016						Yes	Yes	Yes	Yes	Yes
Kroner	2012						Yes	Yes	Yes	Yes	Yes
Reimer	2012						Yes	Yes	Yes	Yes	Yes
Tammam	2009	No	Can't tell	Yes	Can't tell	Yes					

5.5 Results

Searches returned 1164 unique articles after deduplication, with 99 studies included for full text screening. From this, nine studies, published between 2004 and 2019 were eligible for inclusion, representing 609 participants, including 83 participants from five qualitative studies (See PRISMA flow chart, **Figure 9**).

5.5.1 Design, sample size and setting

Table 19 provides a summary description of the included studies. Three studies used questionnaires (415-417), one of which (417) included free text comments. A fourth comprised of researchers' opinion of patients' views (418).

Five studies were of qualitative interviews (419-423). Sample sizes ranged from 61 (418) to 205 (415) for quantitative studies, and 10 (419) to 23 (423) for qualitative studies. Four studies were in outpatient settings (415-417, 420), three in inpatient settings (418, 419, 423) and two in the community (421, 422). Studies were conducted in the USA (415, 416, 419), Canada (421), Australia (417, 422), Germany (420), Norway (423) and England (418).

Figure 9: PRISMA flow diagram

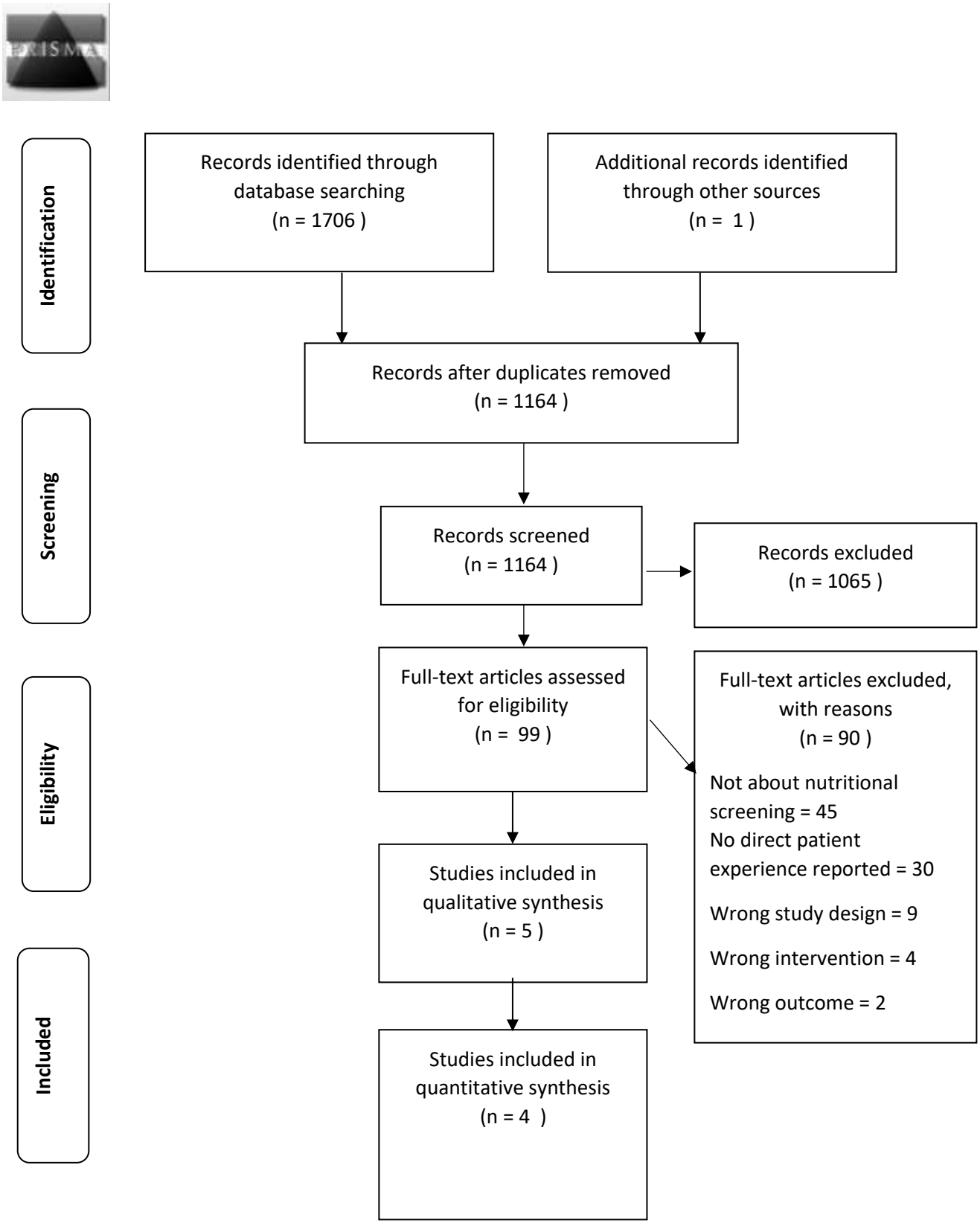


Table 19: Study characteristics summary

Quantitative studies	**Method of data collection**	**Age, years**	**Sample size, Sex**	**Diagnosis and setting**	**Nutrition screening tool**	**Recruitment**
Cawood, 2012 USA (415)	Questionnaire, % results	18–87 YO Mean 55	n= 205 F= 90 M= 115	Outpatients; gastroenterology, surgical, medical, oncology, urology, and gynaecology clinics	MUST; self-screen and HCP screen	Approximately every third person in clinic; 72% consented to involvement
Cawood, 2018 USA (416)	Questionnaire, % results	Mean 50.4 ± 16.2	n= 100 F= 43 M= 57	Outpatients; gastroenterology, medical, oncology or surgical clinics	MUST; self-screen and HCP screen	Next available patient in clinic, HCP recruitment
Di Bella, 2018 Australia (417)	Questionnaire, written comments	Mean 58 ± 16	n= 160 F= 67 M= 93	Outpatients; receiving systemic supportive therapies or radiotherapy	MST; patient-led and dietitian-led	Consecutive patients
Tammam, 2019 England (418)	Participants questioned regarding assessment	> 18 YO	n=61	Inpatient; medical, surgical and oncology wards	INSYST I & II by nurse, MUST, MNA by researcher	Convenience sample
Qualitative studies	**Method of data collection**	**Age, years**	**Sample size, Gender**	**Diagnosis and setting**	**Nutrition screening tool**	**Recruitment**
Callen, 2004 USA (419)	Qualitative interviews, naturalistic qualitative evaluation methods of Guba and Lincoln (1981)	≥65 YO Mean 74 ± 6.6 Range 68–86	n= 10 F= 4 M= 6	Inpatients; acute services. Nutritional risk identified with DETERMINE tool	DETERMINE Level 1 screen by dietitian	Convenience sample

Kroner, 2012 German (420)	Qualitative interviews, Mayring, (2008) content analysis	Mean 63 Range 37–84	n= 12 F= 5 M= 7	Outpatients, receiving chemotherapy	PG-SGA	Not stated
Reimer, 2012 Canada (421)	Qualitative interviews	>55 YO	n= 22 F= 13 M= 9	Free-living in community, members of senior's association; classed as at risk by SCREEN II tool	SCREEN II	Random sample; SCREEN II via post
Hamirudin, 2016 Australia (422)	Qualitative, in-depth interviews	≥ 75 YO	n= 17	Free-living in community; classed as 'at risk' or 'malnourished' by screening tool	MNA-SF	Opportunistic screening; GP practice
Balstad, 2019 Norway (423)	Structured de-briefing interviews	Mean 64.4 YO ± 11.9	n= 23	Inpatients n=22, Outpatient n=1, n=22 receiving anti-cancer treatments	PG-SGA	Purposive sampling

Key: DETERMINE (DETERMINE Your Nutritional Health), HCP (Health Care Professional), INSYST I & II (Imperial Nutritional Screening System I & II), MNA (Mini Nutritional Assessment), MNA-SF (Mini Nutritional Assessment Short Form), MST (Malnutrition Screening Tool), MUST (Malnutrition Universal Screening Tool), PG-SGA (Patient Generated Subjective Global Assessment), SCREEN II (Seniors in the Community – Risk Evaluation for Eating and Nutrition), YO (years old)

5.5.2 Participants

Participants with a range of medical conditions were represented, including those receiving medical or surgical treatments (415, 416, 418, 420, 423) including anticancer treatments, such as chemotherapy and radiotherapy (417, 420, 423), and free-living individuals without significant morbidity (421, 422). Various recruitment methods were used, including consecutive (416, 417) and sequential (415) inclusion of clinic patients, and convenience (418) sampling of inpatients in quantitative studies. Qualitative studies used convenience (419), random (421) opportunistic (422) or purposive (423) sampling. One study did not state recruitment methods (420). No papers were identified which captured experiences of patients' families or informal carers.

Various malnutrition screening tools were used; Malnutrition Universal Screening tool (MUST) (415, 416), Malnutrition Screening Tool (MST) (417), Imperial Nutritional Screening System I and II tools (INSYST I & II), Mini Nutritional Assessment (MNA) (418), DETERMINE Your Nutritional Health (DETERMINE) checklist (419), Patient Generated Subjective Global Assessment (PG-SGA) (420, 423), Seniors in the community – Risk Evaluation for Eating and Nutrition II tool (SCREEN II) (421) and the Mini Nutritional Assessment – Short Form (MNA-SF) (422). See **Table 19**.

5.5.3 Questionnaire findings

Three studies (415-417) collected data regarding participant's experiences of screening using questionnaires. The fourth (418) evaluated the acceptability of the tool by asking participants their subjective opinions regarding the tool. From these, most participants reported they were agreeable towards nutritional screening, with 99% (415) and 100% (416) of participants in two studies reporting they were happy to answer questions regarding their nutrition. Written comments (417) included three positive responses, of screening as a 'good idea', and four negative comments, suggesting nutritional screening was 'unnecessary'. Requests for explanation of screening results were made (415). Finally, the fourth study (418) where comments from participants were noted, suggested most were comfortable with the screening process and recognised the importance of screening.

5.5.4 Interview findings

Three key themes emerged: 1) experience of nutritional screening; 2) misunderstanding of malnutrition; and 3) barriers to, and opportunities for change.

5.5.4.1 Experience of nutritional screening

Comments regarding screening tool content or process were common, with data generating a theme regarding the acceptability of being screened. Participants found screening to be simple

(419, 422), and possible as part of a routine assessment (421) Questions asked were acceptable, and participants did not feel they were too sensitive or intrusive (420, 422).

"Well it's quite simple. When you get to my age, you want things simple don't you?" (422)

However, some participants were unclear on what had been examined, or of the purpose of nutritional screening (420). Completion of questionnaires also caused some participants distress, particularly when discussing unintentional weight loss, or negative changes to their physical condition (423).

"I want to avoid this! [refers to question about weight loss]. The hardest thing is when you lose weight when you actually don't want to" (423)

5.5.4.2 Misunderstanding of malnutrition

A key theme was seen regarding participants misunderstanding of the term malnutrition, with many believing that 'malnutrition' was not following a 'healthy diet', high in fruits, vegetables, and wholegrains, or that being overweight precluded malnutrition (419-421):

"I'm 280 pounds. How can I be malnourished?" (419)

This requirement to follow a 'healthy diet' was reinforced by the media (e.g. magazines), and family members, if participants had received a new medical diagnosis (e.g. cancer) (420, 422). Participants had a poor understanding of malnutrition and its contributory factors; with participants reporting that their overall nutritional health was 'fair' or 'good', even if screening showed a nutritional issue to address (419).

"Well I couldn't understand that. When I eat properly – I feel I eat properly – I couldn't understand why… then it showed I was malnourished" (422)

Due to this misunderstanding, some participants reacted negatively when informed of their nutritional risk, and were disappointed or upset with screening results (421, 422). Some felt accused of having an inadequate diet (421), or having a poor knowledge of nutrition when they believed they were well-informed (419).

"I was initially kind of shocked that I scored… you know" (421)

"So in what way do you feel I… I'm not doing the right things?" (421)

This caused participants to justify their current dietary intake, and describe how they had cut down on 'bad' foods, and were making an effort to consume the 'right' foods, including changing snacks to fruit, consuming wholegrain foods, or reducing red meat intakes (419-422).

"Yeh well I eat loads of vegetables and so I found it ah… I am doing things right" (421)

"Now I eat fruit instead of chocolate" (420)

Risk perception

Further misunderstandings of malnutrition's causes and consequences were seen in participants who had lost weight. Participants saw weight loss as a positive, due to previously being overweight (420), and rationalised weight loss as due to healthy dietary changes, rather than their diagnosis. Weight loss was also seen as a normal part of ageing (422), and was not associated with disease (420).

"Yes, I noted it [weight loss], I'm better off, I was a bit too snug" (420)

However, some participants credited weight loss as a cause of physical weakness, and saw weight loss as a negative event (420, 423)

"I have lost a lot of weight, seven kilos, it was the end of my strength. It [weight loss] was bad and depressing" (420)

Due to beliefs that being overweight, or following a 'healthy' diet precluded malnutrition, participants did not see themselves as 'at risk'. With this, nutritional screening results were not prioritised, and advice to manage malnutrition was declined or ignored (421, 422). Participants also compared their own risk to others, feeling their risk was comparatively low; this was supported by a perceived lack of symptoms related to malnutrition (421).

"I don't feel I'm as much at risk as… as the community at large. And that's what bothers me are the people out there. They're far more at risk I feel" (421)

Symptoms, such as weight loss were seen as a normal part of ageing, or the disease process (e.g. cancer), and therefore were not seen as modifiable (420, 422)

"Well they can't do much. It's me getting old, tired and worried and well, you know" (422)

Results of screening

Reactions to results of screening varied. On reviewing results, rather than focusing on nutritional risk, participants noted positive aspects of their current diet (421, 422). A focus on 'room for improvement' was seen; with screening results seen as affirmation of aspects of their diet they were getting 'right' rather than highlighting areas which required intervention (419, 421).

Similarly, participants often dismissed results or advice, as weight loss was attributed to other perceived unrelated factors, such as cancer therapies, or a belief that their current knowledge or actions were sufficient (420, 422);

"I don't need it. No, we look after ourselves as far as cooking and eating is concerned. I think common sense has got a lot to do with it" (422)

Interpretation of nutritional risk was also contextualised in light of other health concerns or social situations (419-421), particularly if participants felt they were eating well (419, 422), therefore dietary changes were not a priority.

"Well because of the issues I have with my son and his children, I didn't really take an awful lot of notice of it I'm afraid. I'm sorry, I should have but I didn't" (422)

5.5.4.3 Barriers to, and opportunities for change

Barriers to change, misinformation and rejection

Several barriers to changing dietary intake emerged. Results of screening were dismissed as irrelevant, incorrect or unrequired (420-422) if participants felt they were eating well, or were consuming a 'healthy' diet, and resulted in participants declining information aimed at improving their nutritional status (422).

"Well I couldn't understand that. When I eat properly – I feel I eat properly – I couldn't understand why… then it showed I was malnourished" (422)

Poor appetite, caused by ageing or diseases status, was a barrier to change (419-421). Similarly, social circumstances and lifetime habits, such as cooking and food choices, also presented as barriers, meaning nutritional information was not prioritised above other concerns or habits (421, 422).

Nutritional recommendations were also rejected due to participants feeling information provided was not personalised, and methods and results of mass nutritional screening were not applicable to themselves as individuals.

"The recommendations were good for the average person, but like I said, I believe that I eat and watch my diet quite well" (421)

Opportunity for change

Conversely, some participants were pleased the topic of nutrition was addressed, and felt they may benefit from nutritional recommendations (420-422). However, this was often seen as "room for improvement" (419, 421), rather than a requirement to change.

"I count on the medical profession to let me know if they see that there is something wrong. If my weight drops or whatever, then I hope they will ring bells and say "Hey!" (421)

5.6 Discussion

We provide the first systematic review and synthesis of patients, families, and carers' experiences of nutritional screening. Results of this review suggest participants found nutritional screening to be acceptable. Despite this, issues regarding the relevance, understanding, and value of nutritional screening must be noted. Reaction to results of screening were mixed, and included disbelief, disappointment, and offence, as well as being seen by some as an opportunity for learning. Poor understanding of malnutrition, misattribution of risk, and perceived barriers contributed to low prioritisation and indifference to results and nutritional advice given.

Although survey responses suggest nutritional screening is perceived as an acceptable process, and completion of screening tools themselves was not burdensome, analysis of qualitative papers regarding the usefulness and applicability of nutritional screening raise questions regarding nutritional screenings effectiveness.

Qualitative and survey responses align regarding the acceptability of the screening process; however, some participants did not understand the purpose of screening, or what was being screened for. Similarly, results showing risk of malnutrition were met with disbelief or indifference, as malnutrition, and the role of screening were not well understood, and therefore were not prioritised. This lack of understanding of malnutrition and its role in ageing, disease and overall health, meant participants expressed little concern regarding a diagnosis of malnutrition risk; with perceptions of good nutrition focused on following a 'healthy' diet, rather than one appropriate for their current medical condition. Importantly, generic nutrition support advice was often rejected, as participants perceived themselves to either require individualised advice, e.g. due to comorbidities, or did not see themselves as one of the majority.

Common barriers to change included incorrect assumptions that weight loss and poor appetite were a normal part of ageing, or an expected part of disease. A recent systematic review (424) identifying barriers and facilitators to nutritional screening in the community, which included both patient and HCP responses, identified similar barriers, including; reluctance to be screened, lack of recognition of malnutrition and its importance, and avoidance of 'unhealthy' calorie-dense foods. Moreover, our review suggested perceptions regarding the positives of weight loss and avoidance of 'unhealthy' foods were reinforced by family and media encouragement to follow a 'healthy' diet.

Mass nutritional screening is recommended as per NICE (138), however, its benefit has yet to be evidenced. A Cochrane review examining the effectiveness of nutritional screening on

patient outcomes and quality of care found that there was insufficient evidence in the support of screening, although no evidence of ineffectiveness was found (425). Similarly, NICE guidance recommending nutritional screening is solely based upon expert clinical opinion, and the effectiveness of nutrition support to manage malnutrition risk is unclear, as previous studies demonstrated little overall effect on mortality, and carried a high risk of bias (138, 404, 426). Considerations of the cost-effectiveness and validity of methods of screening are also required when appraising the appropriateness and viability of screening methods, and include the condition being screened for showing benefit of treatment, and the benefits weighed against possible harms caused by screening, e.g. anxiety, overdiagnosis (402, 427).

Concerns regarding the harms of screening are more often considered when discussing screening for diseases such as cancer, where harms of testing procedures, diagnostic false-positives, and anxiety caused by screening itself, are more tangible (405, 426). However, potential harms of nutritional screening, identified by this review, include the distress of being informed of results, particularly if participants felt they were following a 'healthy' diet, or the screening tool highlighting negative physical attributes e.g. significant weight loss. This may cause resistance to change, or reluctance to accept advice to manage nutritional risk. With the lack of evidence regarding the role and benefit of screening, and results of this review suggesting screening results are poorly understood, question regarding the effectiveness of nutritional screening, whilst public understanding of the condition is poor, must be considered.

5.6.1 Implications for clinical practice, research, and policy

This review identified several areas which require further considerations when implementing nutritional screening programmes. Foremost, knowledge regarding malnutrition; both its causes and consequences, must be addressed to allow informed interpretation of screening results. Primarily, misconceptions that weight loss is always a positive health outcome, and that consumption of calorie-dense foods is always 'unhealthy', must be addressed.

Education for vulnerable groups regarding the role of nutritional screening, malnutrition, and its causes and consequences, combined with a tailored approach to providing nutritional advice may help support behaviour change, particularly in societies where key public health messages are aimed at combatting obesity.

With this, further research regarding the most appropriate and effective interventions to identify and manage malnutrition should be conducted to prevent psychological or physical distress when there is no prospect of benefit, e.g. anxiety or disbelief of results resulting in disengagement, or provision of inappropriate treatments e.g. for patients with refractory cachexia (428).

How to alter public health messages, to encompass requirements for different nutritional needs across the lifetime, and between the two public health considerations of obesity and malnutrition, also requires consideration.

5.6.2 Strengths and limitations

Use of a mixed-methods design is a main strength of this review, with both qualitative and quantitative studies included in the analysis. This allowed triangulation of results and enabled a richer insight into patients' experiences of nutritional screening.

Although this review only included nine studies, the depth of information gained from the 5 included qualitative studies, which included 83 participants, regarding the specific topic of nutritional screening, provides a robust assessment of patients' views of nutritional screening (429). However, due to limitations identified in the original articles, including some limited sample sizes, and lack of diversity in research populations, caution is required when interpreting results, and further research regarding patients' experiences of nutritional screening is required.

Additionally, we did not use a theoretical framework underpinning the qualitative analysis. However, due to the narrow topic and small number of studies included, the absence of a framework is unlikely to have weakened results.

Studies included in this review were from high income countries, where issues of obesity, its associated comorbidities, and the requirement for weight loss to manage these conditions, is a key public health message. Therefore, the generalisability of some findings (e.g., weight loss seen as positive) may be limited to societies were obesity is felt to be a greater concern than malnutrition.

5.7 Conclusion

Misunderstanding, caused by a lack of knowledge regarding the causes and consequences of malnutrition, resulted in reduced risk perception and disbelief or rejection of screening results. Nutritional screening can be a trigger for dietary changes, but barriers, including older age, lifetime habits, disease status and social factors, particularly family and media encouragement of 'healthy' diets, meant nutritional problems were not prioritised, particularly when weight loss, and poorer dietary intake were seen as a normal part of ageing and the disease process. This resulted in low prioritisation of screening results and associated recommendations. The effectiveness and appropriateness of nutritional screening, when results are misunderstood, and risk misattributed to disease or ageing, must be considered, particularly when the efficacy of nutritional interventions to manage malnutrition are unknown. Although the process of screening is acceptable, without addressing patient barriers, particularly a fundamental lack of knowledge regarding malnutrition, in the context of a paucity of cost-effectiveness data, the role of nutritional screening must be questioned.

5.8 Summary

This chapter presented the methods, results and discussion of a systematic review of patient, family, and carer experiences of nutritional screening. In this review, the results of nine studies, representing 609 participants, with 83 participants from five qualitative studies, were synthesised. Although screening for nutritional problems was seen as 'acceptable', a lack of understanding regarding the causes and consequences of malnutrition resulted in low prioritisation, or disregard of screening results. Findings also suggest that nutritional concerns are not prioritised in relation to other aspects of health, with several barriers to acceptance of nutritional screening and provision of advice identified. In the next chapter, **Chapter Six**, the methods for the mixed-methods observational study will be presented.

Chapter 6: Mixed-Methods Study: Methods

Chapters four and five presented the findings of the systematic reviews, showing the relationships between markers of malnutrition and clinical outcomes in older adults with cancer **Chapter Four**, and patients' experiences of nutritional screening **Chapter Five**.

Due to the clinical overlap between malnutrition, sarcopenia, and cachexia, particularly in older adults with cancer who are at a higher risk of all three conditions (12, 13), the ability to differentiate between, and therefore effectively diagnose each condition is challenging. To facilitate the aim of producing a single tool that can achieve this, I designed a mixed-methods observational study. This involved screening older adults with cancer, aged ≥70 years, for sarcopenia, cachexia, and markers of malnutrition, and recording their subsequent clinical outcomes. Qualitative interviews, regarding the process of screening, and patient views, experiences, and opinions on screening, and of the three conditions, were also conducted.

Due to the COVID-19 pandemic; delays caused by having to close and restart the study in between COVID-19 waves, and difficulties with recruitment caused by the pandemic, amendments were made to adapt and modify the study. The original study aim and objectives are outlined in **Appendix 1**, with the original study protocol, which outlines the intended study design is shown in **Appendix 2**. **Figure 10** shows the original study design, and **Figure 11** details the amended mixed-methods study design.

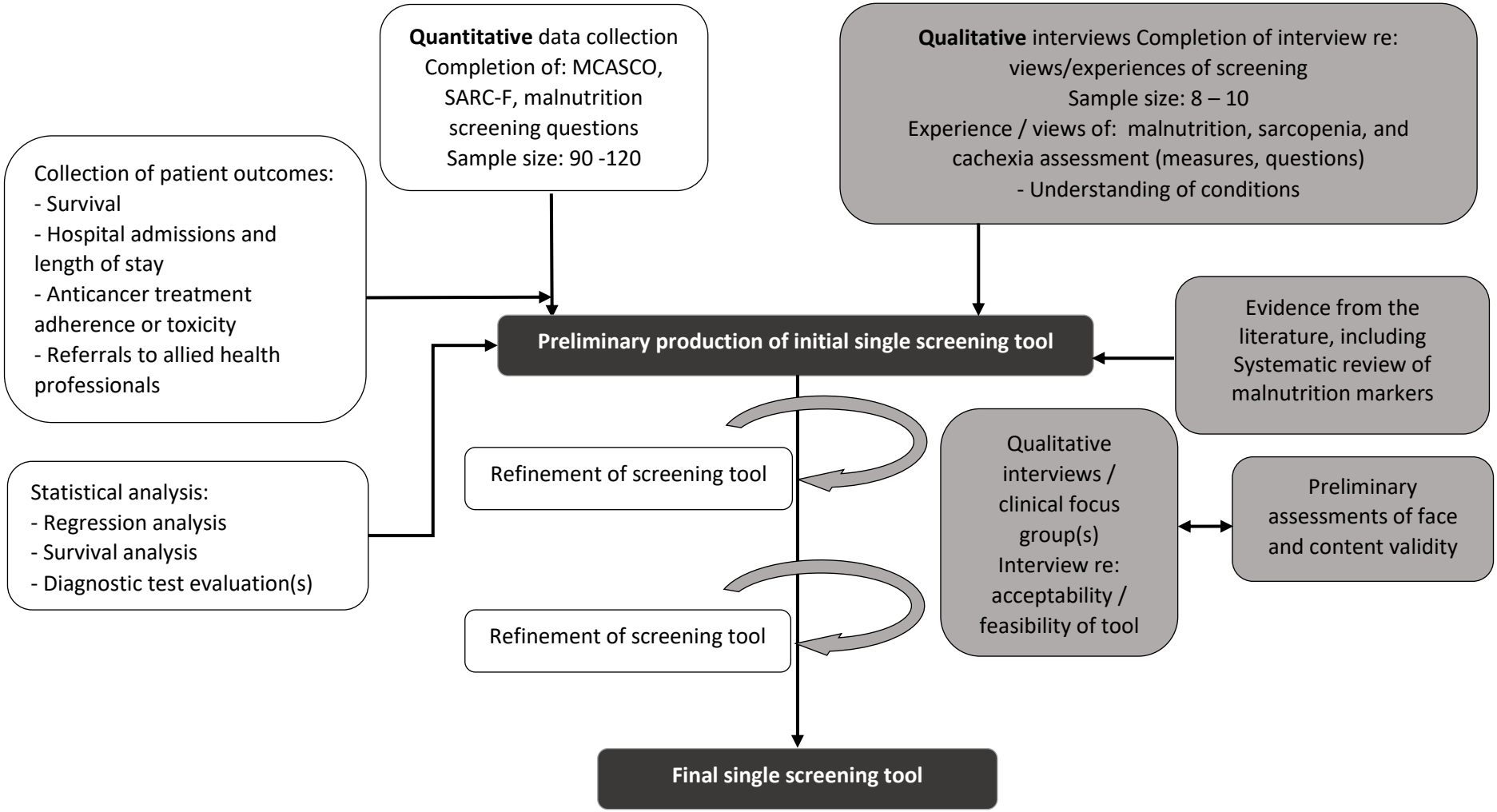


Figure 10: Diagram detailing the original mixed-methods, observational cohort study with a convergent parallel design

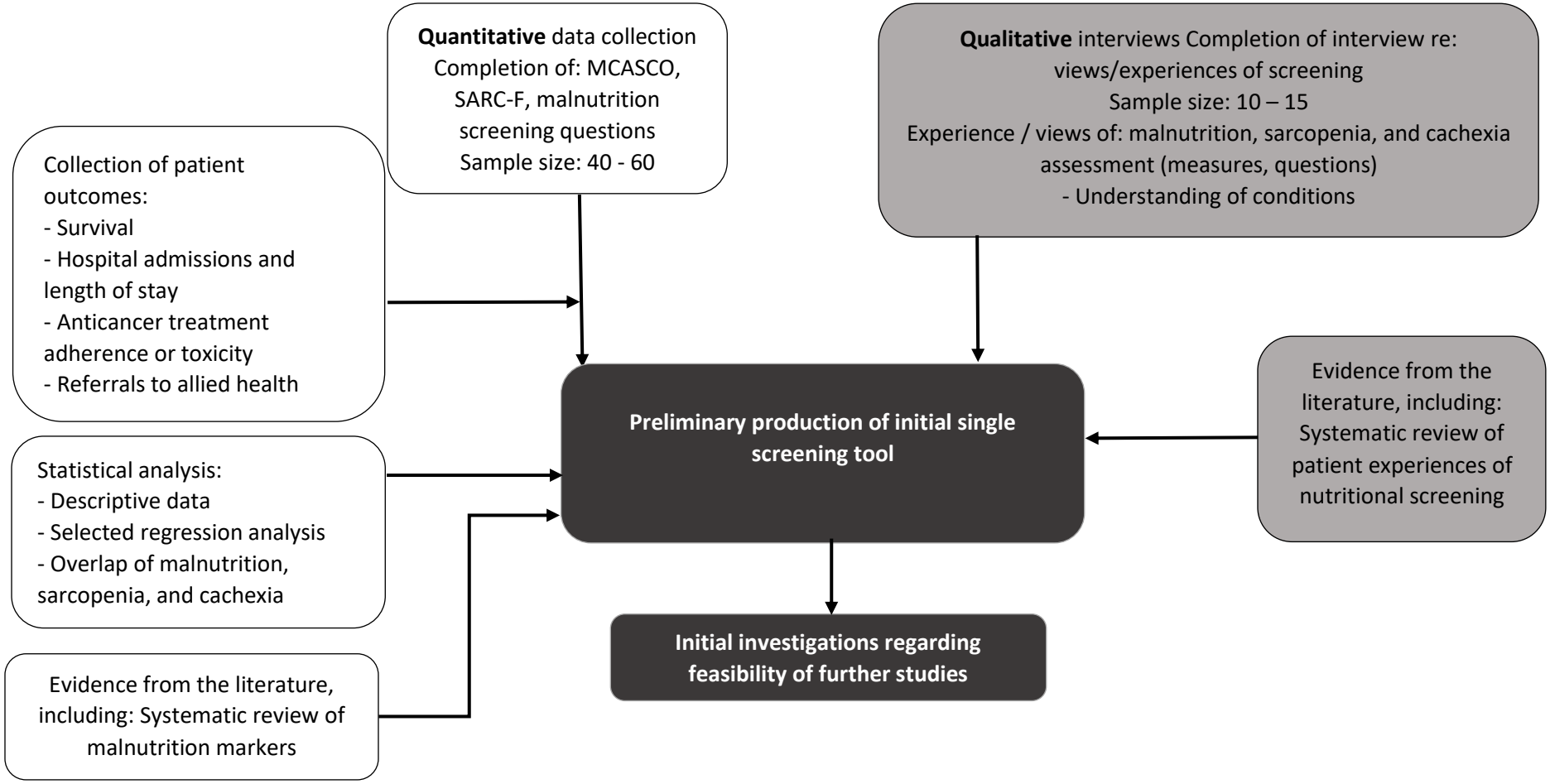


Figure 11: Diagram detailing the amended mixed-methods, observational study with a convergent parallel design

6.1 Study objectives and designs

The changes to the study objectives and associated study methods are discussed below.

6.1.1 Study research questions

The research questions to be answered by the quantitative data collection and analysis were:

- Which markers of malnutrition, sarcopenia, and cachexia used in screening tools are predictive of clinical outcomes in older adults with cancer?

However, due to the impact of the pandemic, this became unattainable, this was amended to:

- What is the prevalence and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer?

A mixed-methods approach was required to achieve my overall aim, therefore the study also included qualitative interviews, with data collected in parallel with the observational study. The research question for the qualitative data collection was:

- What are the experiences and views of older adults with cancer regarding screening for malnutrition, sarcopenia, and cachexia?

Data collected were to be used to inform on the feasibility, clinical relevance, and patient acceptance and perceived benefit of a screening tool to detect and differentiate between malnutrition, sarcopenia, and cachexia in older adults with cancer.

Due to time and resource limitations within the scope of this thesis, validation of the screening tool was not possible. Additional original research questions, regarding the acceptability and feasibility of a single screening tool by patients and clinicians, and assessment of the statistical properties of said tool, were planned, but were not completed due to delays and recruitment restrictions caused by the COVID-19 pandemic. Study questions, their methods, and how they have been affected are detailed in **Table 20**.

Table 20: Table of study aims, questions and research objectives amended due to the pandemic

	Original research aim/questions	Amended research question
Overall research aim		
Research aim	Develop a single, clinically relevant screening tool, able to identify and distinguish between elements of malnutrition, sarcopenia, and cachexia in older adults with cancer	To understand better the prevalence, detection, assessment, and patients' experiences of malnutrition, sarcopenia, and cachexia in older adults with cancer.
Research questions		
Question:	Which markers of malnutrition, sarcopenia, and cachexia used in screening tools are predictive of clinical outcomes in older adults with cancer?	What is the prevalence and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer
Objectives:	To explore the relationship between malnutrition, sarcopenia and cachexia and clinical outcomes	To gain exploratory estimates of the prevalence of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer
	To assess the statistical properties of the new tool as proof of concept	To explore the interrelationships and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer
	To explore the acceptability and feasibility of the new tool by patients and clinicians	To investigate the feasibility of conducting a subsequent adequately powered study to develop, refine, and test, a single, clinically relevant screening tool, able to identify and distinguish between elements of malnutrition, sarcopenia, and cachexia in older adults with cancer
Method:	Cohort study	Cross-sectional study
Question:	What are the experiences and views of older adults with cancer regarding screening for malnutrition, sarcopenia, and cachexia?	No change
Objective:	To explore patients experiences and views of clinical assessment and management of malnutrition, sarcopenia, and cachexia	To explore and understand patients' experiences and views of the clinical assessment and management of malnutrition, sarcopenia, and cachexia
Method:	Patient participant interviews	No change

6.1.2 Study design

I conducted a mixed-method, single centre study, with a convergent parallel design. This was an exploratory observational study, with both quantitative and qualitative aspects running in parallel. Participants receiving inpatient and outpatient care at the Queens Centre for Oncology and Haematology (QCOH) were screened for malnutrition, cachexia and sarcopenia using the SARC-F sarcopenia screening tool (109), MCASCO cachexia screening tool (16), and nutritional screening questions and assessments (18). Interviews with a sub-sample of these participants regarding their experiences and views of nutritional screening, was also conducted. Clinical outcome data were collected at baseline, and at three-, six- and 12-months, to explore the relationship between the presence of these three conditions on participants' outcomes, e.g., survival data, adherence to planned cancer treatment. However, due to the impact of COVID-19 on clinical outcomes, these were not used in the analyses. The results from the screening tools and interviews were used to inform upon the feasibility, clinical relevance, patient acceptance and perceived benefit of developing a single, clinically relevant, shortened screening tool to distinguish between elements of the three conditions simultaneously so management plans could be appropriately targeted.

I had planned further stages, to explore patients' and clinicians' opinions regarding the acceptability and feasibility of use of the singular screening tool, which included participant interviews regarding the use of the screening tool. Responses were to be used to further shape and refine the tool. However, as noted previously, due to delays and issues caused by the COVID-19 pandemic, not all aspects of the study could be completed within the thesis timescale. **Figure 12** outlines the proposed study timeline; and **Figure 13** for the actual study timeline. See section **6.7** for the impact of the COVID-19 pandemic on the study.

6.1.3 Patient and public involvement

Patient and public involvement (PPI) is recommended to improve the relevance and quality of research (430), with members of PPI groups contributing through discussion to decisions about research, of its design, relevance, conduct, and acceptability (430). The proposed protocol, study measures, topic guides and lay information were presented and discussed at the Trans Humber Consumer Research Panel – a local panel led by lead clinical research therapist at HUTH, which included members of the public with experiences of a wide range of medical conditions and/or experience as a carer for relatives with chronic conditions. See **Appendix 8** for the panels feedback form. See section 6.6.2 for discussion of changes made. Further discussions of the proposed protocol, study measures, and topic guides were then completed with a member of the public with experience caring for a loved one with cancer. See section **6.6.2.**

<table>
<tr><td>Jan
2020</td><td>Feb
2020</td><td>Mar
2020</td><td>Apr
2020</td><td>May
2020</td><td>June
2020</td><td>July
2020</td><td>Aug
2020</td><td>Sept
2020</td><td>Oct
2020</td><td>Nov
2020</td><td>July 2021</td></tr>
<tr><td colspan="7">Cohort study – quantitative data collection</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td colspan="6">Interviews – qualitative interviews</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">Production of shortened screening tool</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">Initial refinement of single tool</td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="8">Collection of longitudinal outcome data: three-, six-, and twelve-month follow-up (April 2020 – July 2021)</td></tr>
</table>

Figure 12: Original timelines for data collection, analysis, and longitudinal follow-up

<table>
<tr><td>Jan 2020</td><td>Feb 2020</td><td>Mar 2020</td><td rowspan="4">Study suspension</td><td>Oct 2020</td><td>Nov 2020</td><td rowspan="4">Study suspension</td><td>May 2021</td><td>June 2021</td><td>July 2021</td><td>Aug 2021</td><td>Sept 2021</td><td>Oct 2021</td><td>Nov 2021</td><td>Mar 2022</td></tr>
<tr><td colspan="3">Group one
Pre-COVID
13/01/2020 – 13/03/2020, n=30</td><td colspan="2">Group two
COVID
19/10/2020 – 19/11/2020, n=6</td><td colspan="5">Group three
COVID
17/05/2021 – 30/09/2021
n=3</td><td></td><td></td><td></td></tr>
<tr><td></td><td colspan="2">Interviews
Group one
10/02/2020 – 13/03/2020, n=3</td><td colspan="2">Interviews
Group two
19/10/2020 – 19/11/2020, n=2</td><td colspan="5">Interviews
Group three
17/05/2021 – 30/09/2021
n=3</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">Analysis to inform upon single screening tool</td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="12">Collection of longitudinal outcome data: three-, six-, and twelve-month follow-up for groups one and two, and three- and six-month follow-up for group three. Follow up complete March 2022.</td></tr>
</table>

Figure 13: Actual timeline for data collection, analysis, and longitudinal follow-up

6.2 Methods of quantitative data collection

The following section details the study inclusion and exclusion criteria, baseline demographics collected, screening questions and measures, and patient outcomes collected, including details of the various methods of data collection. See section **3.2.1** for the rationale for the chosen population, and section **3.4.8** for the rationale of chosen screening methods.

6.2.1 Participants

Participants were eligible for inclusion if they were:

- Aged 70 years and older;
- Multi-disciplinary team (MDT) agreed diagnosis of one of the following cancer diagnoses;
    - Breast cancer
    - Colorectal cancer
    - Lung cancer
    - Prostate cancer
    - Head and Neck cancer
    - Upper Gastrointestinal cancer
- Able to provide informed consent;

Participant exclusion criteria were:

- Those considered by the MDT to be in the last few weeks of life;
- Unable to understand English well enough to provide fully informed consent, or comply with the study assessments, and suitable translation services are not available were excluded
- Participants on other clinical trials were assessed on a case-by-case basis.

6.2.2 Measures and outcomes

Demographics and clinical measures were recorded at baseline, with clinical outcomes recorded at three-, six- and twelve months. Methods of data collection are detailed in **Table 21.** Additional measures, of participants COVID-19 status, and any previous recorded positive COVID-19 nasal swabs were also included upon the resumption of the study, after the first study suspension.

Table 21: Outcome and demographic data collection methods

Method of collection	Outcomes	Demographic measures
Lorenzo*, electronic clinical record	Survival (original primary outcome) Presence/absence of registration of death, date of death (number of days post measures)	Age
	Hospital admission(s) and associated length of stay (defined as number of 24-hour stays) Referral to Allied Health professionals Dietitians, Occupational therapists, Physiotherapists, Speech and Language therapists (original secondary outcomes)	Sex, Past medical history
ARIA oncology information system**	Anticancer treatment prescription Recorded anticancer treatments (number of fractions of radiotherapy, planned chemotherapy, number completed Anticancer treatment adherence Documentation of breaks in treatment, cancellation, or postponements Anticancer treatment toxicities Identified through patient journal entries	Cancer diagnosis Including TNM status
Patient report		Social history Employment, smoking status, cohabitation/carers
Clinician assessment		Rockwood clinical frailty scale score (431) Charlson comorbidity index (432)

Additional measures, of participants COVID-19 status, and any previous positive COVID-19 nasal swabs were also included upon the resumption of the study after the first study suspension.

*Lorenzo: Hull University NHS Trust Generic electronic health record

** ARIA: Hull University NHS Trust Oncology specific electronic health record

6.2.3 Screening measures

Measures of; the diagnosis of malnutrition, sarcopenia, or cachexia, were determined from the data collected, as outlined in **Table 22.** All measures were collected at baseline. All measures were taken, and questions were asked of participants by me as the researcher. See **Appendix 9** for the data collection form. I demonstrated all physical study measures, including measurement of mid-arm circumference, use of handgrip dynamometer, chair stand test and timed-up-and-go (TUG) test, and use of Bioelectrical Impedance Analysis (BIA) to study participants before measures were taken. Participants were able to decline any screening measures or questions they did not wish to, or were unable participate in, or answer. The reason for declining the measure was recorded. **Table 23** outlines the nutritional screening questions asked, including associated anthropometric measures, against the published malnutrition screening tools.

6.2.4 Primary and secondary outcomes

The original primary and secondary outcome measures are denoted in **Table 21**. Due to the impact of the pandemic, the use of these measures was no longer feasible, see section **6.1.2**. Therefore, diagnosis of the conditions of interest; malnutrition, sarcopenia, and cachexia, were used as primary outcomes.

Alongside the outcomes, additional assessment of the feasibility of measures; of patient's ability to complete the measure or of patient's choice to decline to complete the measure, were also noted.

Table 22: Markers of malnutrition, sarcopenia and cachexia and associated data collected by assessment domain

Marker	Malnutrition	Sarcopenia	Cachexia
Anthropometry	Weight: current, three, six and 12 months ago; Height: BMI; Mid-arm circumference; Hand-grip strength; Fat-free muscle index; Visual assessment: clavicles, temples, emaciated	Hand-grip strength; Chair-stand test; Fat-free muscle index; Timed-up-and-go-test; Qu: difficultly carrying 10lb; Qu: difficulty walking across a room; Qu: transferring chair to bed; Qu: difficulty 10 stairs; Qu: falls in one year	Weight loss; Fat-free muscle index; Qu: effort climbing stairs; Qu: fatigue walking 500m; Qu: stay in bed/chair; Qu: limitations in work/daily activities; Qu: felt weak
Biochemical	NA	NA	Albumin;Haemoglobin; C-reactive protein; Lymphocyte count
Clinical	Diagnosis; Comorbidities	NA	Qu: pain; Qu: physical/medical condition interfering with family life; Qu: rate overall health; Qu: rate overall QOL
Dietary	Diet texture: normal (solids), soft diet, liquid only, minimal; Oral intake: ONS / EN / PN / NBM; Percentage of meal(s) eaten: 100%, 75%, 50%, 25%, <25%; Assistance with eating: no, some, complete; Fluid intake; gastrointestinal problems: oral, pain, oral dryness, difficulty swallowing, nausea and vomiting, constipation/diarrhoea	NA	Qu: appetite; Qu: when I eat, fullness
Environment	Food preparation: Self, NOK/partner, family member, carer, other; Food shopping: Self, NOK/partner, Family member, carer, other	NA	Qu: limitation in work/daily activities; Qu: limitation to hobbies/leisure activities; Qu: need to rest; Qu: pain interfering with activities; Qu; difficulty concentrating

Key: BMI = Body Mass Index, EN = Enteral Nutrition, NA = not applicable, NBM = nil by mouth, NOK = next of kin, ONS = Oral Nutritional Supplements, PN = Parenteral Nutrition, Qu = question

Table 23: Malnutrition screening tool questions by corresponding published screening tool

Malnutrition screening question	**Corresponding screening tool**	**Value / answer**
Current weight, 'usual weight' and weight loss, Intentional weight loss	BAPEN, BNST, CNST, ESPEN, GNRI, INSYST, MST, MUST, NRI, NRS-2002, NUFFE, SGA, SNAQ, SNST, 3-MinNS	Percentage overall loss, timeframe of weight loss, Yes / no unintentional
BMI (weight / height^2)	BAPEN, BNST, ESPEN, MUST, NRS-2002, 3-MinNS	kg/m^2
MAC	BAPEN	cm
FFMI	ESPEN	kg/m^2
Visual assessment: Temple	3-MinNS	Hollowing / slight depression / defined
Visual assessment: Clavicles	3-MinNS	Protruding / slight protrusion / not visible
Visual assessment: Emaciated	SNST	Yes / No
Assessment of appetite	NUFFE, SGA, SNAQ	Yes / No Time periods decreased
Type of oral intake	BAPEN, BNST, SGA, SNST	Normal (solids) / soft diet / liquids only / minimal / NBM (if NBM time-period)
Regular use of supplements	SNAQ	ONS / EN / PN
Percentage of meal usually eaten / reduced oral intake	BNST, CNST, INSYST, MST, NRS-2002, NUFFE, SGA, SNST, 3-MinNS	All, 75%, 50%, 25%, <25%, time-period reduced
Require assistance with eating	NUFFE	No / some / complete
Fluid intake per day	NUFFE	Number of cups / mls per day
Gastrointestinal symptoms: Oral	NUFFE, SGA	Pain / dryness / difficulty swallowing
Gastrointestinal symptoms: Nausea and vomiting	SGA	Yes / no
Gastrointestinal symptoms: Diarrhoea or constipation	NUFFE	Yes / no
Who completes food shopping	NUFFE	Self / NOK / Family member / carer / other
Biomarker: Serum albumin	CONUT, GNRI, NRI, PNI	g/l
Biomarker: Total lymphocytes	CONUT, PNI	µ/l
Biomarker: Cholesterol	CONUT	mmol/l (18, 331)

Key: FFMI = Fat Free Mass Index, MAC = Mid Arm Circumference, NBM = Nil By Mouth, NOK = Next of Kin.

Screening tools key: BAPEN = British Association for Parenteral and Enteral Nutrition, BNST = British Nutrition Screening Tool, CNST = Canadian Nutrition Screening Tool, CONUT = Controlling Nutritional Status, ESPEN = European Society for Clinical Nutrition and Metabolism, GNRI = Geriatric Nutritional Risk Index, INSYST = Imperial Nutrition Screening System, MST = Malnutrition Screening Tool, MUST = Malnutrition Universal Screening Tool, NRI = Nutrition Risk Index, NRS-2002 = Nutrition Risk Screening, NUFFE = Nutritional Form for the Elderly, PNI = Prognostic Nutritional Index, SGA = Subjective Global Assessment, SNAQ = Short Nutritional Assessment Questionnaire, SNST = Simple Nutrition Screening Tool, 3-MinNS = 3 Minute Nutrition Screening

6.2.5 Screening equipment

Screening for malnutrition, sarcopenia, and cachexia involved anthropometric measures, blood biomarkers, and collection of demographic information including clinical diagnoses, as noted in **Table 22.** Equipment and methods used to gain the required measures are detailed in **Table 24**. The rationale for, and reliability of these measures, are discussed in **3.4.8**.

Table 24: Screening equipment and associated measures

Equipment or source of data	**Associated measure**
Bioelectrical Impedance Analysis machine	Fat free mass Appendicular skeletal muscle and skeletal muscle index (17, 281, 282) Weight Body Mass Index
Hand-grip dynamometer	Hand-grip strength (kg)
Stadiometer	Height (cm)
Tape measures	Mid arm circumference (cm)
Stopwatch	Timed up and go test Chair stand test
Lorenzo – blood tests	Albumin Haemoglobin Lymphocyte count C reactive protein
ARIA - diagnoses	Cancer diagnoses and TNM status

6.3 Recruitment

Participants were recruited from the Queens Centre for Oncology and Haematology (QCOH), at the Hull University Teaching Hospital NHS Trust (HUTH) from the 13th January 2020. Due to the COVID-19 pandemic, recruitment was suspended on the 16th March 2020. Recruitment reopened on 19th October 2020 but was again closed on 19th November 2020 due to a second COVID-19 wave. Recruitment opened for a third time from 17th May 2021 until 30th September 2021.

Participants were initially to be recruited from inpatient settings, on the oncology wards; 30, 31 and 32, at QCOH, and from oncology outpatient clinics at the centre. However, due to the COVID-19 pandemic, of challenges recruiting from outpatients, combined with HUTH Trust COVID-10 guidance for researchers, this was amended to inpatients only for the second and third study reopening. See section **6.7** for the impact of the pandemic on the study.

The methods for identifying and approaching participants, including consenting for involvement, and study follow up for the quantitative measures are detailed:

6.3.1 Sampling methods

Convenience sampling was used for participant recruitment. To minimise bias, a systematic method was used for identifying and approaching inpatients. For this, inpatients on the medical oncology wards at QCOH were screened by age and clinical diagnosis on the hospital electronic health record, Lorenzo. Next, the current medical condition of potential participants was checked, either *via* the hospital information system, or through discussion with the ward MDT, to check to determine eligibility. As per protocol, participants who were too unwell, or who were considered to be in the last few weeks of life by the MDT were not approached. Potential inpatient participants who met the inclusions criteria were approached for involvement.

Convenience sampling of hospital outpatients was also attempted. Potential participants were identified prospectively from clinic lists, and approached, as able before their clinic appointments. However, due to the changes employed by the Hospital trust, required due to the pandemic, and minimising additional bodies in outpatient clinical areas, approaching patient participants in outpatients during the second and third study reopening's was not possible. Instead, the focus for the second and third groups was changed to inpatients who were willing to partake in both the quantitative measures and qualitative interviews. Participants were still approached consecutively, but with only participants consenting to both aspects of the study recruited in group three. This is discussed further in section **6.7**.

6.3.2 Identification, approach and consent

During recruitment, potential participants were screened against the eligibility criteria before being approached. As I held an honorary clinical contract at HUTH, participants were approached directly by myself for involvement in the study. For this, I introduced myself, explained my role, introduced the study, and explained why the potential participant had been approached. If, at this point, the potential participant wished to hear more about the study, further information regarding the required study measures, expected time commitment, and follow up information to be collected was detailed. Interested potential participants were provided with a copy of the participant information sheet. At this time, potential participants could choose if they wished for me to return at a later agreed time to further discuss any aspects of the study, or, if participants wished, they could move directly to consenting for their involvement in the study. Throughout, the voluntary aspect of the study, the right to suspend involvement at any time, and the fact that their involvement, or choice to decline involvement in the study would not affect their medical care in any way, was made clear to potential participants during the process.

If potential participants agreed to be involved in the study, written or witnessed verbal consent was gained before the collection of study measures. If participants were unable to sign the consent form for any reason, the form was witnessed by another health care professional in QCOH. Opportunities to ask questions or have any points of the study clarified were offered throughout the consenting process. For this, as well as upholding ethical practices as a clinician, I also undertook National Institute for Health Research 'Good Clinical Practice' training, to ensure the rights, safety and wellbeing of study participants were upheld (433).

Copies of the signed consent forms were made, with one copy being provided to the participant, another added to the participants' medical notes, and a copy held securely by the researcher.

6.3.3 Withdrawal or death

Participants were free to withdraw from the study at any time. Participants did not have to provide a reason for withdrawal. Data collected prior to withdrawal of consent were used. Participants who withdrew from the screening measures were asked if any prior consent to participate in an interview still stood, and if researchers may still access routinely collected clinical record data, for the purposes of follow-up. The following information was to be collected if a participant withdrew;

- Date of withdrawal;
- Level of withdrawal (full/partial);
- Reason for withdrawal if participant is willing to provide;

The following information was collected in the event of death;

- Date of death;
- Cause of death (if documented).

6.3.4 Group sample size and sampling

Several considerations were required regarding the sample size original sample size target. As the primary outcomes in this study were binary, an *a priori* sample size was estimated using the methodology presented in Peduzzi et al (434). For this, 10 participants per independent variable for logistic regression is recommended to minimise type I ('false positive') and II ('false negative') errors. Based upon the current literature of the prevalence of malnutrition, sarcopenia, and cachexia in this population at 34%, 38.6%, and 40%, respectively (22, 77, 156), and with expected feasible recruitment rates, of three to four participants per week, for the proposed recruitment period totalling 30 weeks, resulted in a target sample size of 90 – 120 participants. This would have allowed inclusion of three to four variables per model whilst maintaining 10 events per variable (434).

It is noted that, although 10 events per variable (EPV) are commonly used in the development of binary logistic regression models, there is debate regarding the validity of this criterion (435). The use of 10 EPV is particularly debated for the use of predictive models, with the relationship between EPV and model performance somewhat dependent on the methodology used to develop the model; there are concerns that the 10 events per variable rule may be too lenient when using regression analysis for prediction models (435-437), or too strict in some scenarios, such as when using more modern methods of data analysis e.g., those that use data

shrinkage, such as least absolute shrinkage and selection operator (LASSO) (436). However, despite this, few alternate methods for estimating sample size for use in regression analysis have been posed (436). Therefore, to determine the appropriateness of this method of sample size calculation, and to allow inferences from these analyses to be contextualised as well as to drive future development of the tool, post-hoc power calculations were to be performed.

6.3.4.1 Recruitment monitoring

To monitor recruitment, actual recruitment rates were assessed weekly against targeted recruitment rates. Recruitment monitoring was also used to aid the assessment of the feasibility of conducting a subsequent adequately powered study to refine a single screening tool for the three conditions.

Monitoring of study recruitment rates quickly showed the impact of the pandemic once the study reopened for a second and third time. These reduced recruitment rates necessitated the changes in the study aims, and impacted upon methods of recruitment, as previously described.

6.3.5 Quantitative data analysis

Initial data analysis methods were designed for an expected sample size of 90 to 120 participants. This recruitment rate was achieved for the first 10 weeks. However, after the study suspension and restart in October 2020, study recruitment rates fell to one to two participants per week, and fell further when the study reopened in May 2021. Due to this, study data analysis methods were amended. See **Appendix 10** or the original planned data analysis methods, which included regression analysis, survival analysis (including Kaplan-Meier analysis) and diagnostic test evaluation (including receiver operating characteristic (ROC) curve analysis). The amended data analysis methods used are detailed below.

6.3.5.1 Study data analysis plan

Due to the impact of COVID-19 upon patient clinical outcomes, the limited testing for COVID-19, and associated limited recordings of a diagnosis of COVID-19 infection, quantitative data gathered in groups two and three were at high risk of confounding from COVID-19. Similarly, all longitudinal follow up data were also at risk of confounding, therefore could not reliably be used when COVID-19 was a confounder for which I could not control. Because of this, a decision to only use the cross-sectional data obtained from group one, was made. See section **6.7**.

Primarily, diagnoses of malnutrition, sarcopenia, and cachexia were the primary outcomes of interest. Descriptive results, and comparison of groups or assessments of variable relationships, e.g., using t-tests, or chi-squared tests, were appropriate, for example,

independent t-test for comparison of dependent (outcome, scales) variables with independent (exploratory, nominal [binary]) variables. Investigation of the relationships between outcomes and variables were also appropriate, e.g., with use of correlation coefficients and odds ratios.

Odds ratios were calculated from 2 x 2 contingency tables using STATA. Associated confidence intervals and p-values were calculated using the Woolf approximation (438), as this has been shown to be most appropriate for use in small sample sizes (439) on logistic regression confidence intervals for odds ratios with small sample sizes.

With the sample size of 30 participants from group one, following Peduzzi et al., (434), it was possible to conduct a small number of univariate regression models with specifically chosen variables, using both the current literature, and the results of the qualitative aspects of the study to refine the choice of these variables.

6.3.6 Missing data

Although every effort was made to collect all required data, missing data were a possibility, particularly in relation to study measures that may be unfeasible for older populations. Missing data were to be dealt with in two ways;

Initially, I planned to use list-wise deletion (the removal of the entire participant record from the analysis is a single value is missing). Therefore, statistical models were to be built using participants with complete data sets. Multivariable models would thus have been completely nested; where one model is a subset of a larger model. This would have ensured that likelihood-ratio tests, which compare the 'goodness of fit' of the models to determine which model is most predictive of an outcome, were valid. Secondly, if missing data were 'missing at random' (440) multiple imputation could also have been used; replacing missing data with several imputed plausible substituted values based on the data we can observe, with the number of imputations chosen to ensure the stability of the results (5). As a form of sensitivity analysis, statistical results would have been compared between models built on the imputed data and those built on non-imputed data.

Noting of missing data will also contribute to the formation of the single screening tool. A qualitative assessment of the feasibility of data collection for each marker or measure is required to aid the formation of the tool, as the clinical utility of the tool relies upon the ability to gain all required markers or measures. As I was collecting and collating all data for this study, missing data were at a minimum; with the only missing data relating to participants declining to answer or complete study measures.

6.4 Methods for qualitative data collection

The initial study plan for the mixed-methods study included initial interviews with patient-participants, followed by interviews or focus groups with clinicians, and further patient-participant interviews, during the refinement of the screening tool. However, due to the impact of the COVID-19 pandemic on the study timeline, this last stage became unachievable to complete in the timeline of my PhD. Therefore, only patient-participant interviews were completed. The sections below outline the methods for the patient interviews. **Appendix 11** details the planned methods for the interviews and focus groups with participants and clinicians, which were planned to refine the screening tool.

6.4.1 Interview recruitment

Regarding qualitative interviews, participants were asked before signing the consent form for involvement in the quantitative aspect of the study if they would like to be contacted for interview. This was rechecked at the end of the initial study data collection, and if participants continued to consent to involvement, contact details were taken. Participants were contacted for interview within seven days of completion of study measures, with participant interviews occurring between two and 10 days after initial study data was collected. Participants who were visited at home, or who were coming into QCOH for interview were contact 48 hours prior to the interview to confirm their ongoing willingness, and ability to complete the interview. Due to the COVID-19 pandemic, and changes to the processes of data collection, participants interviewed in the second and third groups were either interviewed by telephone, or whilst still present as an inpatient at QCOH, to minimise the risk of COVID-19 transmission, and minimise additional patient visits to QCOH.

6.4.2 Interview sample size

An estimated sample size of 10 to 15 patient participants was planned, based upon the theory of information power (301); topics covered within the interview, as outlined in the topic guide (see **Appendix 12**), were narrow and focused on the exploration of patient views, experiences, and understanding of assessments for malnutrition, sarcopenia, and cachexia, as well as the conditions themselves.

6.4.2.1 Sampling method

One of two methods of sampling were planned, depending on participant uptake to interviews. If a majority of recruits consented to involvement, purposive sampling, using the below frames (see **Appendix 13**) was to be used (289). However, due to difficulties in recruitment, convenience sampling, of inclusion of all participants who volunteered to interview, was used.

6.4.3 Interview data collection

The following section outlines the process for data collection for the qualitative interviews. Once patients were approached, had the study process explained, received study documents, and consented to involvement in the study, data collection began first with the completion of quantitative study measures (see section **6.2**). Then, for those who had consented to interviews, the additional process for qualitative data collection was undertaken. For those who had consented to an interview, the process was explained prior to the start of the interview, and participant agreement to complete an interview was reconfirmed. All interviews were conducted using a topic guide (see **Appendix 12**) and voice recorded using a password protected Olympus DS-9000 digital voice recorder. Due to the inductive process of the interviews, the topic guide was used as a framework, and adapted as interviews progressed. The following process was used for the interviews:

Introduction:

- Re-introducing myself if there was a delay between interview and quantitative data collection, including reintroducing the study;

- Key points: purpose and length of interview, voluntary nature of interview, recording of interview, including participant ability to pause or stop the interview or decline to answer any questions, confidentiality, and opportunity for the participant to ask questions. Confirming consent to interview.

Interview:

- Main objectives included: exploring participants' experiences and views of any previous assessments of malnutrition, sarcopenia, or cachexia, and the study assessment for the three conditions. Participant understanding of the three conditions, and the role of the three conditions in relation to cancer.

Interview conclusion:

- Concluding interview, including asking participants if they had any additional comments;

- Thanking the participant for their time and reminding participant of the confidentiality and anonymity of the interview;

If required, directing participants towards additional services, e.g., psychological support, or health services if any issues were raised during the interview which required management.

6.4.4 Qualitative data analysis

Interviews were voice-recorded and transcribed by myself onto Microsoft word documents. Voice-recordings were anonymised using a study ID only to ensure confidentiality, with all identifying features removed during transcription. Recordings were transcribed verbatim, including filler speech and conventions of dialogue, for full analysis of the context of the language and interaction between participants. Once transcribed, documents were uploaded to NVivo 12; a qualitative data management software tool (441).

The rationale for my choice of thematic analysis is presented in **3.5.2.4**. I used the following steps when analysing the data: Initially, familiarisation with the data, gained through transcription and repeated reading of transcripts was conducted. Once familiarised with the data, initial coding of the data was undertaken by myself, focusing on the participant's experiences and views. Once all transcripts were coded, codes were charted and mapped to allow generation of themes from the data. Double coding of 25% of the transcripts was completed by a fellow PhD clinical fellow and Dietitian (MP), and by my PhD supervisor (MJ) to ensure consistency in coding, gain multiple perspectives, and refine the coding system (442). Codes were linked, and from this, categorised into themes after discussion with the second coder, and PhD supervisor. This process is detailed in five stages:

i. Familiarisation; listening, transcribing, and annotating participant interviews;

ii. Coding; generation of initial codes via systematic analysis, producing succinct, descriptive, interpretive codes, focusing on meanings of lived experience (307). This involved systematically working through the data, interpreting the data, and establishing initial codes;

iii. Searching for themes, developing patterns within the data; using this opportunity to look more broadly at the themes being developed, producing themes and subthemes'

iv. Indexing; naming the themes, identifying what is unique about each theme, avoiding overlap, identifying association with research question;

v. Interpreting; 'telling the story', of how these themes answer the posed research questions (249, 306, 307).

vi. Following the completion of thematic analysis, I subjected the data to loop analysis, see section **3.5.2.5**, by identifying relationships between themes, which when merged, produced a loop diagram (314, 317).

6.5 Ethics and research governance process

The necessary governances were in place prior to data collection. Hull York Medical School ethical approval was received on 24th July 2019 (see **Appendix 14**). Sponsorship was provided by the University of Hull (see **Appendix 15**). Health Research Authority and NHS Research Ethics Approval was given by the London Central Ethics Committee on the 29th November 2019 (see **Appendix 16**). Hull University Teaching Hospitals NHS Trust capability and capacity was confirmed on 17th January 2020 (see **Appendix 17**).

6.5.1 Confidentiality, data management, and archiving

All research data were handled according to GDPR 2016.679 law. Data were stored on a password-protected computer, and appropriately backed up. Participants were allocated a unique study ID for data collection; therefore, all data were anonymised. A master index file linking the study ID with patient identifiable data, for follow up data collection purposes, was held in a separate file on a password-protected computer. An encrypted flash drive was used when transportation of data was required.

Regarding data archiving, study documents will be retained for five years, accessible to authorised researchers only, and will be destroyed after this time. All audio files were deleted after transcription.

6.5.2 Study amendments

Study amendment, required to restart the study due to the study suspension caused by the pandemic are summarised in **Table 25**, with the full impact of the pandemic on the study discussed in section. Study amendments and approvals related to the starting and stopping of the study due to the pandemic are detailed in section **6.7.4**.

Table 25: Study amendments to allow resumption of study

Initial method	Amended method	Impact
Screening of potential participants by age and diagnosis	Screening of potential participants by age, diagnosis and COVID-19 status (nasal swab for inpatients, symptoms for outpatients)	Any COVID-19 positive participants, or those showing symptoms of COVID-19 were not approached for inclusion
Baseline measures taken included patient participant comorbidities, disease status and social support	Baseline measures as prior, additional recording of previous COVID-19 status, identified by previous positive nasal swab	COVID-19 status recorded as possible confounding variable
Follow up measures of survival, hospital admission, anticancer treatments, and referrals to allied healthcare professionals	Follow up measures as prior, with additional recording of COVID-19 status	COVID-19 status recorded as possible confounding variable
Collection of baseline measures at hospital (inpatient ward or outpatient clinic), participants home or the University of Hull	Collection of baseline measures at hospital (inpatient ward or outpatient clinic), or over the telephone	Minimising face to face contact in non-clinical settings
Standard hygiene measures: wiping down of study equipment post use	Additional hygiene measures and use of PPE: researcher to wear PPE as per Trust guidelines. Handwashing before and after collection of study measures. Cleaning of study equipment before and after measures. Participants asked to wear a facemask and either wash their hands or use hand sanitiser before taking part in study measures	Minimising risk of transmission of COVID-19

6.6 Ethical considerations

As with all research, consideration of potential ethical issues, and their mitigation is a key aspect of research. The main ethical considerations of this thesis are discussed here. For this study, there are six main areas that have required ethical consideration: i) consent and withdrawal from the study, ii) inclusion and exclusion criteria, iii) consideration of impact of research measures, iv) result of study measures, and v) access to potential participants, and vi) role of research vs dietitian.

6.6.1 Consent and withdrawal from the study

A core aspect of scientific research is the requirement for voluntary consent and the protection of participants (443). For this, when consenting participants for the study I clearly identified and introduced myself, the purpose, implications, and requirements of the research, and expected time commitments were outlined to the participants. Participant information sheets, tailored to each part of the study as also provided to explain this in further detail, including information on data collection, consent for involvement in study interviews, and right to withdraw from the study. Opportunities to answer any additional questions were provided. Participants were required to initial and sign the consent forms, see **Appendix 18** for participant information sheets and **Appendix 19** for consent forms.

To ensure informed consent is gained; that participants have capacity to consent to involvement, I undertook Good Clinical Practice training (433), and I also have experience working as a clinician and therefore have prior knowledge in gaining informed consent from patients. All participants were given as much time as required to consider their involvement in the study. However, in view of the low risk of the study, if they wish to proceed immediately to perform the study measures, and if this was more convenient for the participant, immediate consenting was used.

For this study, the right to withdraw, pause, suspend or stop study measures and interviews, at any time, is an important issue. Participants involved in this study had cancer diagnoses and were receiving cancer interventions or monitoring. Therefore, participants were often unwell, and considerations of their wellbeing was paramount. To manage this, participants were informed of their right to withdraw, or pause or stop study measures at any time, without the need to provide a reason, but could resume measures, if they wished, within seven days, if they wished to pause the measures due to fatigue.

6.6.2 Inclusion and exclusion criteria

The study inclusion criteria are detailed in section **6.2.1**. The rationale for including older adults, and adults with specific cancer diagnoses are discussed in section **3.2.1**.

One issue which required consideration was the inclusion or exclusion of participants who were approaching the end of life. Initial thoughts were to only exclude patients who were expected to die in the next few days. However, on reflection, this was then amended to exclude all patients in the last few months of life, as active treatments for the three conditions of malnutrition, sarcopenia, and cachexia would unlikely be offered to this group, and screening participants in this stage of life, where no treatment may be offered, was considered unethical. However, the PPI group, when reviewing the study protocol, questioned this. After discussions, this was changed back to only excluding those patients who were in the last few weeks of life, as advice for symptom management, reassurances regarding these conditions, or appropriately tailored interventions, may be provided at any stage of the disease. It was also argued that potential participants would not consent to involvement in the study if they felt it would be too burdensome.

When conducting research with patients who may be receiving palliative care, additional considerations are required. Patients receiving palliative care are considered a vulnerable group, therefore additional safeguarding considerations are needed (444). Recognition of time demands on participants becomes of increasing importance, with involvement in a study potentially taking time away from other preferred activities (444). Also, the results of the research will not provide any direct benefit to those participants involved. However, research has suggested that participants receiving end of life care may perceive benefit by being involved in research, and may see research as an opportunity to contribute to other patients care (445, 446).

6.6.3 Consideration of impact of study measures

In addition to the overall burden of research, the impact of study measures and interviews on participants was considered, this includes time commitments, performance of study measures, and the potential emotional impact.

6.6.3.1 Time commitments

The completion of the study measures is a single contact for patient participants, unless requested by the participant to pause the study measures and recommence at another time. No direct follow-up is required, except for participants who have consented to qualitative interviews.

The decision to avoid repeat measures was carefully considered. The option to bring patient participants back after three months, to repeat measures, was discussed. This was suggested due to the lack of research around the development of cachexia, where repeat measures may show participants decline, and aid prediction of outcomes. However, ethically, conducting

repeat measures with unwell patient participants, particularly those with cachexia, whose symptom burden is likely to become more severe, is ethically questionable. Also, when considering the initial expected sample size; if 30% of participants were diagnosed as cachexic, 27 to 36 people would return for measures, assuming no attrition or mortality. This sample size was unlikely to provide statistically significant results; therefore, the additional participant burden cannot be justified.

6.6.3.2 Performance of study measures

Alongside questions, a range of physical tests, including measures of height, weight, mid-arm circumference, lean body mass by bioelectrical impedance analysis, and physical tests of performance were conducted. Each test was explained to participants prior to completing. Participants were advised not to attempt the measure or test if they felt they were not able to safely complete it. Participants were also able to decline involvement in any measure without providing a reason, but a reason was requested if the patient was comfortable to provide one. These processes helped ensure the physical wellbeing of the participants. Although blood tests results were required as part of the malnutrition and cachexia screening tools, for this study to remain non-invasive, and to also test the feasibility of blood measures, additional blood tests were not taken: the most recent blood test on the Hull University Teaching Hospital (HUTH) computer system Lorenzo were used instead.

6.6.3.3 Emotional impact

Prior to consenting for involvement, participants were briefed on the content of study measures and interviews. It was possible that some of the questions asked during the study measures, or raised during the interviews, may have made the participant think about their cancer. Issues about ability to eat, perform daily activities, quality of life, and other questions may have raised broader issues of psychological distress. Levels of participant distress were closely monitored, and if confirmed by the participant, contact details for support services and health professionals who were available to discuss their concerns in detail were provided. As I have experience working in oncology and discussing potentially sensitive topics with patients, this, alongside forewarning participants of the topics, ensured emotional distress was appropriately managed.

6.6.4 Results of study measures

Participants were screened for cachexia, sarcopenia, and asked malnutrition screening questions. As this was an observational study, I was not aiming to affect or change patient participants usual clinical management, therefore, results of the screening tool assessments were not disclosed to patient participants or their clinicians. The ethical considerations for this are multifaceted. Currently, cachexia and sarcopenia are not screened for at HUTH, and if

diagnosed, no treatment options could be offered, therefore their diagnosis would not impact upon clinical decision making, or the participant's treatment. However, informing participants of a diagnosis for a condition where no treatment can be offered may cause additional concern. For malnutrition, HUTH follow their own protocol for nutritional risk screening; daily screening using their 'nutrition risk screening tool' for inpatients, and screening at initial assessment or upon clinical concern for outpatients. Also, as general malnutrition screening questions, rather than specific tools were used, malnutrition risk would not be able to be communicated at the point of contact.

6.6.5 Access to potential patient participants

Prior to undertaking this study, I worked as a specialist oncology dietitian at QCOH, in HUTH, and worked weekly at this centre, as a dietitian, whilst completing this study. To enable this, I was awarded an honorary contract which provided me with the ability to work clinically as a dietitian – as a usual member of the patient's clinical team, as well as conducting research. This role allowed me to approach potential patient participants as a member of their clinical team directly, rather than requiring a first contact from another member of their Multi-Disciplinary Team (MDT). It also meant that I had access to hospital computer systems, including Lorenzo and ARIA, to allow identification of potential patient participants, and collection of follow-up data and outcomes. Similarly, working relationships with members of the MDT, including ward and outpatient nursing teams, specialist nurses, allied health care professionals and consultants, meant that advocacy from clinicians to potential patient participants aided in study recruitment. However, as discussed below, there is a conflicting role of a researcher and clinician, which has had to be addressed and managed during this study.

6.6.6 Role of researcher *versus* dietitian

As a registered dietitian, I am required to follow an ethical framework, which outlines what is expected from a health care professional (447). For the most part, the standards of conduct, performance, and ethics echo the National Institute for Health Research 'Good Clinical Practice' guidelines, of ethical, scientific and practical standards for clinical research (433). However, patient participants were screened for the three conditions, but neither the patient participants, nor their clinicians were informed of the results. This produces a conflict of aims when working as a researcher, compared to a clinician. The aim of a researcher is often to expand knowledge and understanding, to improve the way clinical care is delivered in the future. However, clinicians aim to treat and manage the health and wellbeing of service users at the point of care. To mitigate this conflict, steps have been taken to ensure a differentiation

of role is seen by patients regarding the position I took. However, personally, changing from a caring, problem-solving role, to a distanced, observing role, was a challenge.

As part of this, considerations of my physical presentation, and how I introduced myself to participants was important. Working as a clinician, wearing a white and blue dietetics tunic and Trust identification badge purveys a clinical role, which may have resulted in patient participants expecting dietetic input. However, wearing non-medical working clothes may have presented an obstacle as I may have not been perceived as part of the medical team. Similarly, how I introduced myself, as a researcher, versus as a dietitian, would also set alternating tones and expectations. For this, making clear in the first instance that no dietetic intervention or changes to treatment, except in the case of clinical concern, was essential. Similarly, a consciousness of the ability to take advantage of these relationships was needed, to avoid inappropriate or unethical participant recruitment.

As this study may have uncovered causes of concern for which clinicians have a duty of care, participants were made aware through the participant information sheet that these issues would be raised with the participant's permission, and permission to contact the participant's general practitioner (GP) in such incidences would be requested. This included social or clinical concerns, or the participants being identified as needing additional medical support.

6.7 Impact of the COVID-19 pandemic

Due to the COVID-19 pandemic, several alterations and, postponements occurred during the study. These, alongside the impact of the pandemic on data analysis, are detailed in the following sections.

6.7.1 COVID-19 timeline

On the 30th January 2020, the World Health Organisation Emergency Committee declared a public health emergency of international concern, in relation to the SARS-CoV-2 epidemic in the People's Republic of China (448). The first case of COVID-19 (SARS-CoV-2) identified in the United Kingdom was on the 31st January 2020, with the first patient to patient transmission recorded on 28th February 2020 (448). On 11th March 2020, the outbreak of COVID-19 was declared as a pandemic by WHO (448).

Following this, UK government guidelines recommended all those aged 70 years or over, those who were pregnant, and those with certain health conditions, to self-isolate (449). Subsequently, a UK-wide enforced lockdown, through the Coronavirus Act 2020, was imposed on the 23rd March 2020 (449). For this, all non-essential travel and work for non-key workers was prohibited (449). Members of the public were only able to leave their homes for medical needs, essential travel to work, to care for others, or to exercise once daily (449). At this time,

social distancing and protocols for the shielding of vulnerable groups were also enforced (449). Full lockdown, initially planned for three weeks, continued for 7 weeks until 10th May 2020, when restrictions eased to allow those unable to work from home to return to work, limited non-essential shops reopened, and meetings of one person outside of their household could meet another outdoors, at a distance of two metres (449). After gradual easing of restrictions, a second national lockdown was imposed on 5th November, and a third on 6th January 2021 due to further COVID-19 waves (449).

6.7.2 COVID-19 and the NHS

During the COVID-19 pandemic, the National Health Service saw an unprecedented increase in demand for beds to manage the COVID-19 crisis (450). At its initial peak, 3,099 patients were admitted in a single day to NHS hospital (450), with critical care bed occupancy peaking at 3,274 beds on 14th April 2020. To free up capacity to enable treatment of patients with COVID-19, multiple areas of the NHS were closed, or had a reduced capacity. The British Medical Association estimate that in April, May and June 2020 there was between 1.32 and 1.50 million fewer elective hospital admissions, and between 2.47 and 2.60 million fewer outpatient attendances in England (451, 452).

A key area that was also affected was the referral for, and initiation of cancer treatments in England. Initial estimates suggest that between 274,000 and 286,000 fewer urgent cancer referrals were seen, with between 32,800 and 40,900 fewer cancer treatments initiated (452). This equates to approximately 42 – 54% of the usual activity in cancer referrals, and 60 – 83% of initiations of cancer treatments, as compared to the April and May 2018-19 averages (452).

6.7.3 Postponement of research

Due to the increasing pressure placed on the NHS, all research activities at the study site; Hull University Teaching Hospitals NHS Trust, were suspended on the 16th March 2020. Only research which investigated the pandemic, or which was classified as urgent health research, where clinical care is research protocol dependant, and the benefits to patient safety of continued participants outweigh the risks of stopping treatment, or research where treatments have the potential to improve the capability for patients to respond to the COVID-19 infection, were continued. This research study was classified by the Trust as 'research where there is no identified positive or negative impact of recruitment/participation continuing". Therefore, as per Trust guidelines, where resources permitted, delivery of the study could continue, but further recruitment was suspended. At this point, 30 patient participants had been recruited, with all baseline information for these participants collected.

Where able, collection of outcome data for these participants could continue to be collected, as resources permitted, however no further recruitment was permitted.

Due to the expected increased demand for NHS services, alongside staff sickness, shielding of vulnerable staff members, and increased demand for clinicians to return to the NHS, with my skills as a qualified Dietitian, experience in oncology and critical care, it was decided that, as no further study recruitment was possible, the study would be suspended, and I would be seconded back to the NHS. To enable this, a non-cost five-month extension for the PhD was requested, with my PhD programme suspended on the 14th April 2020.

The University of Hull, acting as study sponsor, the London Central REC committee, and the Clinical Research Network (CRN) were informed of the suspension of the study on the 23rd March 2020.

6.7.4 Restarting research

My secondment to the NHS ended on the 1st October 2020. To resume the study, protocol amendments were required to enable the safe reopening of the study. Key aspects to be addressed were:

- Participant and researcher safety: minimising risk of COVID-19 transmission;
- Additional cleaning protocols for study equipment: minimising risk of COVID-19 transmission;
- Additional data collection: COVID-19 status of participants.
- All study amendments were related to minimising risk to participants and researchers involved in the study, as well as following Trust protocol regarding the use of personal protection equipment (PPE), accounting for the COVID-19 status of potential patient participants, minimising face to face contact where possible, amendment of study locations for data collection, and collecting data regarding participants COVID-19 status to account for COVID-19 as a possible additional cofounder. Key amendments are summarised in **Table 25**. See **Appendix 20** for the IRAS Amendment Tool. As all amendments were related to changes made due to the pandemic, and no significant changes were made to the study methods, a non-substantive amendment, with no study-wide review required, was requested, and accepted.
- Once amendments had been successfully submitted to IRAS, with the REC committee informed of the above, an appeal to the Trust R&D department, to allow study restart at HUTH was requested. Confirmation of Restart Capacity and Capability at HUTH was

gained on 6th October 2020, with study reopening planned for the 19th October 2020. See **Appendix 21** for confirmation of restart capacity and capability.

However, due to the second wave of COVID-19, and associated second lockdown, a correspondence was sent to all researchers at HUTH on 19th November 2020 requesting all research that was not COVID-19 related, or research with posed risk to patients or affected hospital resources, was to be suspended. Although this study did not detract resources from COVID-related studies, or studies with research protocols that included urgent treatment or interventions without which patients could come to harm, my presence in the hospital increased footfall in inpatient areas and included entering and exiting multiple patient rooms and wards, increasing the risk of COVID transmission. From discussion with my supervisor, and R&D at HUTH, it was decided to re-suspend the study, with an aim to restart data collection in the new year, as circumstances allowed. See **Appendix 22** for HUTH correspondence. During this time, I was again seconded to work in the NHS for a further three months; with a further three-month, non-cost extension to the PhD being put in place (11th January 2021 – 31st March 2021). The study was able to reopen on 19th May 2021. See **Appendix 23** for confirmation of study restart capacity and capability.

6.7.5 Impact of COVID-19 on quantitative data collection and analysis

The following sections detail the impact of COVID-19 and the pandemic on the quantitative data collection and analysis, including the impact of COVID-19 on the risk of sampling bias, and impact on longitudinal data.

6.7.5.1 COVID-19 and sampling bias

A key impact of the COVID-19 pandemic on research has been the risk to research validity due to issues with sampling bias (453). Many health services, including HUTH, saw a reduction in general hospital admissions, including a reduction in the number of inpatient oncology patients, particularly elective admissions, and reduced patient attendance at hospital outpatient clinics (451, 452). This resulted in only those with the more severe illness being accessible to researchers, reducing the representativeness of the sample (453); reducing the generalisability of study results. Additionally, changes in HUTH research policy meant I was also unable to recruit from outpatients for the remainder of the study, further limiting the generalisability of the study results. Despite the easing of restrictions in between COVID-19 waves, this reduction in inpatient numbers continued throughout 2020 and 2021 (451, 452).

6.7.5.2 Physical and psychological impact of COVID-19 and national lockdowns

A further impact of the pandemic, which has affected the validity of the studies quantitative results has been the physical and psychological impact of the COVID-19 pandemic on the study

population, including the impact of the national lockdowns, and stay-at-home orders in place for much of the study duration.

As well as the unfortunate fact that older adults with cancer are more susceptible to severe COVID-19 infection, and see higher mortality rates (454), and the increase in diagnostic delays caused by the pandemic, resulting in later presentations and the expected substantial increase in avoidable cancer-related deaths (455), COVID also affected the day-to-day activities, and mental health of the general public.

National lockdowns, imposing stringent restrictions on travel and social interactions, including 'stay-at-home' orders (449), were particularly tight for those classified as 'clinically extremely vulnerable'; such as those who were undergoing cancer treatments, or who had severe lung conditions, who were advised to shield at home (449). The national lockdowns caused a reduction in physical activity and an increase in sedentary behaviour (456, 457). Additional changes were seen in eating habits, including changes in meal patterns, snacking, and diet composition (457, 458). As sarcopenia, a condition impacted by physical activity, and nutrition and diet, were being studied, the impact of these restrictions and the associated changes in the public's physical activity levels and dietary intake, made data from the 'pre-COVID' participants incomparable to the 'during-COVID' participants.

Additionally, the impact of COVID-19 on the mental health of the nation may have also affected recruitment. A study looking at the mental health impact of COVID-19 on the UK population found that mental distress increased during the pandemic, with higher increases seen in females, with age as a key influencer (459). Another study found that, during the pandemic, particular cohorts were less likely to volunteer to be involved in research, including those aged 60 or over, those with a higher education attainment, and migrant workers (453, 460).

6.7.5.3 Additional confounding variables

Finally, consideration must be made for COVID-19 as an additional confounder in itself. In addition to the impact of the COVID-19 control measures, and the effect of COVID-19 on potential participant recruitment, the disease-effect of COVID-19 itself, and its impact on patient morbidity and mortality in this study is unknown.

For all patients recruited to the study during the pandemic (group two and three), the results of nasal swabs to detect COVID-19 were checked and recorded to comply with hospital infection control procedures, and to help ensure researcher safety. However, presence of prior or subsequent COVID-19 infections was unknown; due to either a lack of testing, or

inaccessible records. Therefore COVID-19 as a confounding variable for patient morbidity or mortality is unknown.

The emerging evidence regarding the associations between COVID-19 and malnutrition, sarcopenia, and cachexia show that COVID-19 itself increases the risk of, and prevalence of malnutrition, sarcopenia, and cachexia in hospitalised patients (461-463). Anorexia, a main component of malnutrition and cachexia (12, 428), is also a component of COVID-19 infection; associated with the symptoms of anosmia and loss of taste, alongside anorexia caused by elevated levels of inflammatory cytokines (461, 462). Similarly, the reduction in physical activity, and associated reductions in muscle strength and function seen during the pandemic (461), regardless of any disease-effect associated with COVID-19 infection and treatment, such as a prolonged intensive care stay and the associated loss of muscle mass (464, 465), are further aetiological factors for all three conditions (12, 428, 466). Further, COVID-19 associated weight loss, related to both anorexia and increased energy requirements due to disease-related inflammation (137, 461), is instrumental in the diagnosis of malnutrition and cachexia (12, 428); all of which increase the potential incidences of the three conditions being studied (461, 463, 464).

6.7.5.4 Management of COVID-19 as a confounder

Considering the discussed issues, a decision was made not to amalgamate the datasets of the pre-COVID group (group one), and the groups recruited during the pandemic (group two and three). The impact of the pandemic on participants' daily activities, social interactions, physical activity, diet, and mood (461, 462), all of which were being studied, meant the groups were non-comparable. This further limited the statistical analysis which could be appropriately conducted with the study results.

It may have been possible to statistically control for COVID-19 as a confounder in this population, if data were collected regarding COVID-19 diagnosis, but as mentioned, this could not reliably be recorded for these participants. Future studies, with improved access to COVID-19 test results likely could control for COVID-19 diagnosis in multivariate models, however larger sample sizes than achieved during this study would be required. Additionally, it was not possible to quantify or measure the impact of national lockdowns on participants physical health.

Due to all of these factors, a pragmatic decision was made to limit analyses to the quantitative data collected before the first lockdown (group one, n=30), with only cross-sectional data used, rather than the longitudinal data, which was at high risk of being impacted by the pandemic.

6.8 Summary

This chapter detailed the methods for the mixed-methods observational study, including the study design, study participants, methods of recruitment, sample sizes and sampling methods, and included information on the impact of the COVID-19 pandemic on the study. Next up, the quantitative study results will be presented in **Chapter Seven**, with the Qualitative results presented in **Chapter Eight**.

Chapter 7: Mixed-Methods Study: Quantitative results

In this chapter, I will present the quantitative results of the mixed-methods cross-sectional study conducted as part of this thesis, for which the methods have been presented in **Chapter Six**. The qualitative results of the mixed-methods study are presented in **Chapter Eight**, with a synthesis of findings presented in **Chapter Nine**.

Overall mixed-methods study aim:

- To understand better the prevalence, detection, assessment, and patients' experiences of malnutrition, sarcopenia, and cachexia in older adults with cancer.

Quantitative research questions

Overarching research question:

- What is the prevalence and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer?

Research questions:

RQ1: Is it feasible to recruit, and screen a group of older adults with cancer for malnutrition, sarcopenia and cachexia?

RQ2: What are the demographics and clinical characteristics of this group of older adults with cancer?

RQ3: What is the prevalence and overlap between malnutrition, sarcopenia, and cachexia, in a group of older adults with cancer?

RQ4: What is the association between malnutrition, sarcopenia, and cachexia, and key clinical characteristics, in a group of older adults with cancer?

Research objectives:

- To gain exploratory estimates of the prevalence of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer
- To explore the interrelationships and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer

Due to the impact of the COVID-19 pandemic, the data were not handled as initially planned. As discussed in chapter six, methods, the reduction in sample size, caused by recruitment challenges during the pandemic, resulted in a smaller than expected sample size. COVID-19 also prevented the combined analysis of all participants recruited. Data are therefore presented in three groups:

- Group one: pre-COVID recruits (13th January 2020 to 13th March 2021)
- Group two: during-COVID recruits; between first and second COVID-19 wave (19th October to 19th November 2020)
- Group three: during-COVID recruits; after the second COVID-19 wave (17th May 2021 and 30th September 2021)

Initial outcomes, including overall survival, hospital admissions and their associated lengths of stay, anti-cancer treatment completion and incidence of toxicity, and referrals to allied health care professionals, were recorded at three-, six- and 12-months for group one and two, and at three- and six- months for group three. However, due to the impact of the COVID-19 pandemic, the significant confounding variables, and their impact upon outcomes including survival and hospital admissions, as discussed in chapter six, methods, the longitudinal results will now not be used in this thesis. See **Appendix 24** for survival data. Instead, cross-sectional data analysis has been presented.

7.1 Quantitative results findings

7.1.1 RQ1: Is it feasible to recruit, and screen a group of older adults with cancer for malnutrition, sarcopenia and cachexia?

7.1.1.1 Recruitment

Study recruitment ran between 13th January 2020 and 1st October 2021, with full-time recruitment for two months between 13th January 2020 and 13th March 2020 (group one), one month from 19th October to 19th November 2020 (group two), and for the final four months between 17th May 2021 and 1st October 2021 (group three). **Figure 14** details the expected versus actual recruitment rates for group one. **Figure 15** outlines the recruitment of each of the groups. Recruitment rates for group one averaged 3.3/week (1 – 5 participants per week). Expected recruitment rates were between 3 and 4 participants per week. For group one, 90 participants met the inclusion criteria (see section **6.6.2**) and were invited to participate, of which 30 were recruited (3:1 recruitment ratio). Recruitment rates for group two remained high (31.6% of those approached), however, due to a reduction in the number of hospitalised patients, an average recruitment rate of 1.3/week (range 0 – 2/week) was achieved. Of 19 potential participants who met the inclusion criteria, six were recruited (31.6% recruitment rate).

Recruitment rates for group three were 0.2/week (0 – 2 participants per week). During this recruitment period, a pragmatic decision was made to only recruit participants who were willing to participate in both the quantitative measures and qualitative interviews. This was made due to the low recruitment rates in groups two and three, increased focus on the qualitative aspects of the study, and the non-comparability of the groups due to the impact of the COVID-19 pandemic, as discussed in section **6.7**.

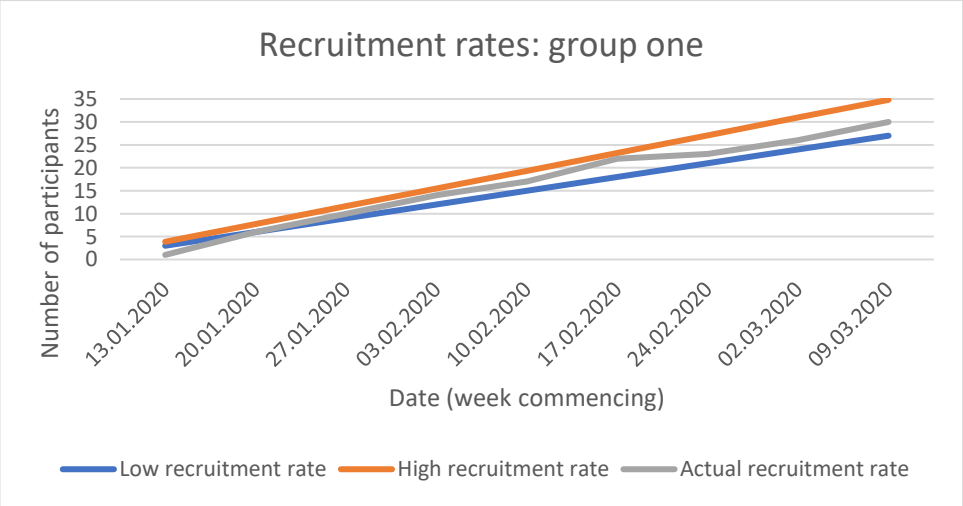


Figure 14: Recruitment rates: expected against actual recruitment rates for group one

Figure 15a

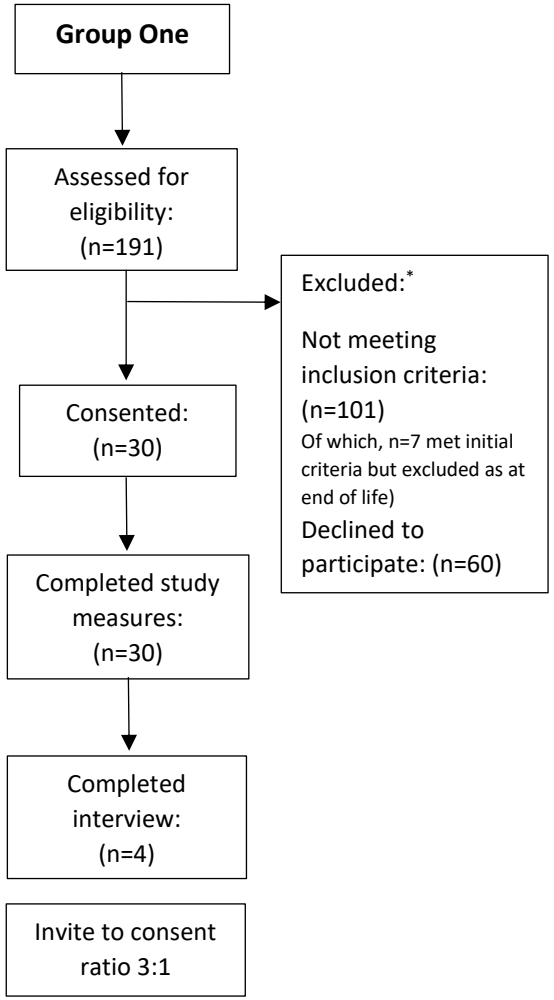


Figure 15b

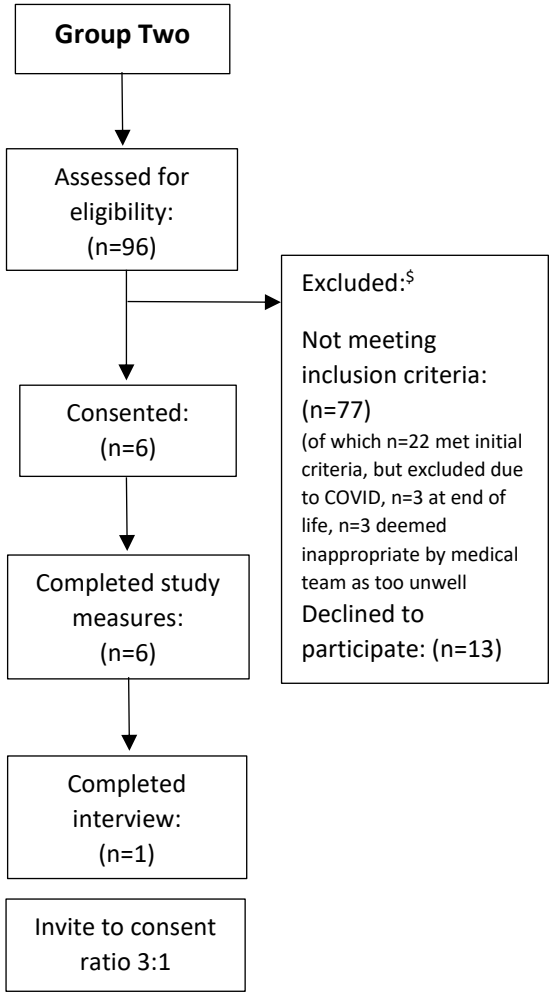


Figure 15c

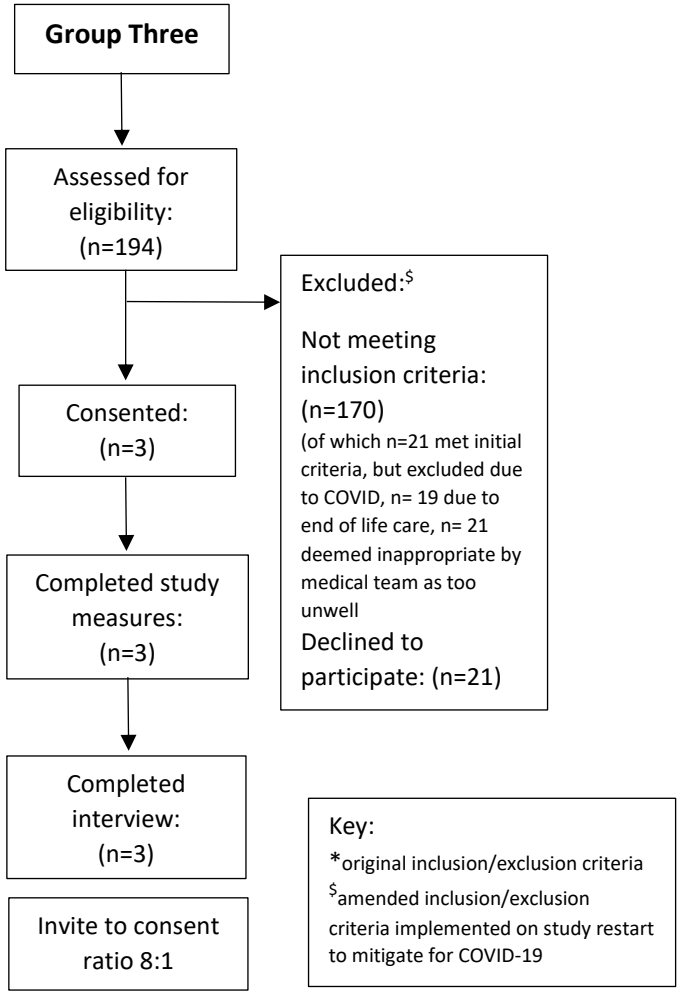


Figure 15: Flow diagram of recruitment for group one (figure 2a), group 2, (figure 2b), and group 3 (figure 2c)

7.1.1.2 Study flow

A total of 39 participants completed the quantitative measures of the study **Figure 15**. Of the screened participants, reasons for declining involvement included: feeling too unwell, felt involvement in the study would be too much, or had no interest in the topic.

From the 39 recruited participants, eight participants consented to, and completed, qualitative interviews; of which six (75.0%) were male.

This study was planned to run continuously, so a 12-month follow-up of all participants was recorded. Due to the suspension in recruitment, 12-month follow-up data are only available for groups one and two, and six-month follow up for group three, due to the time constraints within the PhD thesis. However, due to the impact of the COVID-19 pandemic, as discussed in **Chapter Six**, longitudinal follow-up data were not used in the data analysis. Similarly, data collected in group one were used to answer research questions one, two and three. Data gathered in groups two and three were used in research question one only.

7.1.1.3 Missing data

Missing data comprised 0.55% of screening questions asked. Data were missing on quantifying fluid intake (n=4), perceived ability to walk 500m (n=2), and ability to rate overall health (n=1), or quality of life in the past week (n=1). Reasons for missing data were due to participants being unable to, or declining to, answer specific questions within the screening tools.

7.1.1.4 Study population

The demographic characteristics of the study population are presented in **Table 26**. All study participants were recruited from the inpatient oncology wards at the Queens Centre for Oncology and Haematology. The mean age of the 39 participants was 75.6 years (standard deviation (SD) 4.2). Participant cancer diagnoses were; 35.9% upper gastrointestinal cancer, 28.2% lung, 12.8% breast, 10.3% prostate, 7.7% colorectal, and 5.1% head and neck cancer, of which, 59.0% (n=23) were localised cancer diagnoses. Most participants were male (72.2%, n=26), lived with a partner (76.9%, n=30), with a mean Rockwood frailty index score (measuring fitness and frailty in older adults, on a scale of 1 (very fit) to 9 (terminally ill) of 4.1, and a mean Charlson comorbidity index score (predicting 10-year mortality in adults with comorbidity, with scores ≥5 indicating high risk of death within one year (432)) of 8.1.

Participant clinical characteristics are presented **Table 27**. As can be seen, completion rates were high for all biochemical markers (66.7 – 100%) and most anthropometric measures (greater than 87.2% for height, weight, BMI, mid-arm circumference and hand-grip strength), although chair-stand test (33.3% complete), timed up and go test (30.8%), and bioelectrical impedance analysis (BIA) (41.7%) were notably lower. Hand-grip strength ranged from 7.0 –

39.0kg, chair stand test repeats from 4 – 20 in 30 seconds, and timed up and go ranged from 7.0 to 20.2 seconds. Mean time to collection of biochemical markers was 2.1 days for albumin, 2.1 days for haemoglobin, 2.9 days for C reactive protein, and 2.0 days for lymphocyte count.

Prior to commencing data collection in January 2019, a sample week patient demographic for the Queens Centre's wards was conducted, to allow comparison of the representativeness of the sample gathered. **Table 28** presents admitted patient care statistics between 2019 and 2020 for patients in England, for comparison of recruited and sample populations (**Table 26**).

7.1.2 RQ2: What are the demographics of this group of older adults with cancer?

Table 26: Demographic characteristics of study populations

Demographics	Group One n=30	Group Two n=6	Group Three n=3	All = 39	Sample week
Age: mean (SD), Range	75.7 (4.2) 70 – 83	75.3 (4.7) 71 – 84	77.0 (4.1) 72 - 82	75.6 (4.2) 70 – 84	76.1 (4.8) 70 – 90
Sex: Male	21/30 (70% M)	5/6 (83.3% M)	3/3 (100% M)	29/39 (74.4% M)	20/33 (60.6% M)
Cancer diagnosis					
Breast Lung Prostate Colorectal Head and Neck Upper gastrointestinal	5 8 3 3 1 10	- 2 - - 1 3	- 1 1 - - 1	5 (12.8%) 11 (28.2%) 4 (10.3%) 3 (7.7%) 2 (5.1%) 14 (35.9%)	3 (9%) 5 (15.2%) 12 (36.4%) 5 (15.2%) 1 (3%) 7 (21.2%)
Metastatic cancer Non-metastatic cancer	14 16	2 4	- 3	16 (41.0%) 23 (59.0%)	27 (81.8%) 6 (18.2%)
Social history					
Living with: Partner Family (not partner) Carer Alone	23 2 - 5 -	5 - - 1 -	2 1 - - -	30 (76.9%) 3 (7.7%) - 6 (15.4%) -	
Retired Full-time employed Part-time employed	30 - -	6 - -	3 - -	39 (100%) - -	
Non-smoker Ex-smoker Current smoker	10 20 -	2 3 1	0 1 2	12 (30.8%) 24 (61.5%) 3 (7.7%)	
Rockwood clinical frailty score (1 to 9, well 1; terminally ill 9)					
1 – very fit 2 – well 3 – managing well 4 – vulnerable 5 – mildly frail 6 – moderately frail 7 – severe frail 8 – very severely frail 9 – terminally ill	1 3 8 9 4 4 - - 1	1 1 - 2 2 - - - -	- - - 1 - - 1 - 1	2 (5.1%) 4 (10.3%) 8 (20.5%) 12 (30.8%) 6 (15.4%) 4 (10.2%) 1 (2.6%) 0 (0.0%) 2 (5.1%)	
Charlson comorbidity index score (mild 1–2; moderate, 3–4; and severe, ≥5)					
5 6	6 4	3 1	- -	9 (23.1%) 5 (12.8%)	

7	4	-	-	4 (10.2%)	
8	1	-	-	1 (2.6%)	
9	8	-	-	8 (20.5%)	
10	2	2	1	5 (12.8%)	
11	3	-	2	5 (12.8%)	
12	1	-	-	1 (2.6%)	
13	-	-	-	-	
14	1	-	-	1 (2.6%)	

Table 27: Clinical characteristics of study populations

Clinical characteristics	Group One	Group Two	Group Three	All
Anthropometrics - Mean, SD, Range, % completion				
Weight, kg	76.5 (17.0) 40.9 – 112.9 29/30 (96.7%)	69.9 (12.7) 50.4 – 82.0 6/6 (100%)	65.3 (13.0) 47.0 – 76.1 3/3 (100%)	74.5 (16.4) 40.9 – 112.9 38/39 (97.4%)
Body mass index, kg/m^2	25.4 (3.5) 16.0 – 34.6 29/30 (96.7%)	23.8k (3.9) 18.6 – 27.4 6/6 (100%)	22.3 (4.2) 17.3 – 27.5 3/3 (100%)	24.9 (4.5) 16.0 – 34.6 38/39 (97.4%)
Midarm circumference, cm	27.6 (4.3) 17.5 – 34.0 28/30 (93.3%)	25.1 (4.1) 18.5 – 29.5 5/6 (83.3%)	22.3 (3.7) 20.0 – 29.0 3/3 (100%)	27 (4.3) 17.5 – 34.0 36/39 (92.3%)
Hand grip strength, kg	21.8 (7.7) 7.0 – 39.0 26/30 (86.7%)	26.7 (4.6) 22.0 – 32.0 5/6 (83.3%)	21.7 (3/8) 16.3 – 23.7 3/3 (100%)	22.3 (7.2) 7.0 – 39.0 34/39 (87.2%)
Chair stand test, repeats	10.4 (4.8) 6 – 20 10/30 (33.3%)	10.7 (6.1) 4 – 16 3/6 (50%)	- - 0/3 (0%)	10.5 (4.9) 4 - 20 13/39 (33.3%)
Timed up and go test, seconds	12.4 (3.2) 8.4 – 16.9 9/30 (30%)	12.8 (6.7) 7.0 – 20.2 3/6 (50%)	- - 0/3 (0%)	12.5 (3.9) 7.0 – 20.2 12/39 (30.8%)
Appendicular skeletal muscle, kg (from BIA)	22.5 (4.6) 14.7 – 32.2 12/30 (40%)	23.6 (5.7) 18.1 – 31.4 3/6 (50%)	- - 0/3 (0%)	22.7 (4.7) 14.7 – 32.2 15/36 (41.7%)
Skeletal muscle index, kg/m^2 (from BIA)	7.5 (1.3) 5.6 – 9.8 12/30 (40%)	8.3 (3.2) 6.9 – 10.3 3/6 (50%)	- - 0/3 (0%)	7.7 (1.4) 5.6 – 10.3 15/36(41.7%)
Biochemical markers – Mean days, SD, Range of days from collection, % completion, Mean value, range				
Albumin	2.3 (2.5) 0 – 10 days 29/30 (96.7%) 29.8g/L (20-42)	1.0 (1.3) 0 – 3 days 6/6 (100%) 26.3g/L (20-30)	2.5 (0.3)* 2 – 3 days 2/3 (66.7%) 29g/L (28-31)	0 – 10 days 2.1 (2.3) 37/39 (94.9%) 29.2g/L (20-42)
Haemoglobin	2.2 (1.9) 0 – 7 days 29/30 (96.7%) 116g/L (71-155)	6/6 (100%) 0 – 3 days 1.2 (1.3) 115g/L (87-141)	2.5 (0.3)* 2 – 3 days 2/3 (66.7%) 123g/L (87-168)	2.1 (1.8) 0 – 7 days 37/39 (94.9%) 116g/L (71-168)
C reactive protein	3.2 (3.2) 0 – 11 days 26/30 (86.7%) 49.1mg/L (1-303)	1.5 (1.8) 0 – 4 days 6/6 (100%) 51.6mg/L (4-129)	2.5 (0.3)* 2 – 3 days 2/3 (66.7%) 29.7mg/L (4-70)	2.9 (2.9) 0 – 11 days 34/39 (87.2%) 47.9mg/L (1-303)
Lymphocyte count	2.2 (1.9) 0 – 7 days 28/30 (93.3%) 0.89x 10*9/L (0.26-2.28)	1.2 (1.3) 0 – 3 days 6/6 (100%) 0.73x 10*9/L (0.27-1.55)	0.92 (0.1)* 2 – 3 days 2/3 (66.7%) 0.93x 10*9/L (0.49-1.55)	2.0 (1.8) 0 – 7 days 36/39 (92.3%) 0.8x 10*9/L (0.26-2.28)
Clinical scales – Mean, SD, Range, % completion				
Rockwood clinical frailty scale	3.9 (1.4) 1 – 9 30/30 (100%)	3.5 (1.6) 1 - 5 6/6 (100%)	6.7 (2.1) 4 – 9 3/3 (100%)	4.1 (1.8) Score 1 – 9 39/39 (100%)
Charlson comorbidity index	8.0 (2.4) 5 – 14 30/30 (100%)	6.2 (2.5) 5 – 10 6/6 (100%)	10.3 (0.5) 10 – 11 3/3 (100%)	8.1 (2.5) Score 5 – 14 39/39 (100%)

*Noted likely affected by blood tube shortage August 2021 to end of data collection

Table 28: Office for National Statistics admissions by diagnosis 2019 – 2020

Diagnosis	Total hospital admissions	Admissions aged 70+ years of age	Percentage of admissions
Breast	230,944	52,003	16.2
Lung	133,132	69,330	21.6
Prostate	80,002	47,260	14.7
Colorectal	178,758	79,574	24.7
Head and Neck	42,165	13,068	4.1
Upper gastrointestinal	120,026	59,757	18.6

It is noted that ONS 2019 data included all hospital admissions – admissions presented are not specific to medical-only admissions. HUTH Trust has specialist surgical Upper Gastrointestinal, Colorectal, Breast, Head and Neck and Urology and Thoracic wards, which were not included in this study.

7.1.3 RQ3: What is the prevalence and overlap between malnutrition, sarcopenia, and cachexia, in this group of older adults with cancer?

Table 29 outlines the prevalence of malnutrition, sarcopenia, and cachexia, by screening tool or diagnostic criteria. Of the malnutrition screening tools, 3-MinNS identified 43.3% of group one as at severe risk of malnutrition, the PG-SGA 42.3% as severely malnourished, and MUST 39.3% as at high risk of malnutrition.

For sarcopenia, the SARC-F screening tool identified sarcopenia in 66.7% of group one, with the EWGSOP2 criteria diagnosing sarcopenia in 48.2%. Both the MCASCO and Fearon cachexia criteria identified 56.7% of the group with cachexia.

Table 29: Prevalence of malnutrition, sarcopenia, and cachexia

Condition and Screening tool / Criteria	**Group One n %**
Malnutrition: severe risk	
3-MinNS screening tool	13/30 (43.3)
PG-SGA screening tool	13/30 (43.3)
MUST screening tool	11/28 (39.3)[$]
Malnutrition: moderate or severe risk	
3-MinNS screening tool	18/30 (60.0)
PG-SGA screening tool	23/30 (76.7)
MUST screening tool	15/28 (53.6)[$]
Sarcopenia	
EWGSOP2 criteria	13/27 (48.2)[$]
SARC-F screening tool	20/30 (66.7)
EWGSOP2, with SARC-F used in place if EWGSOP2 missing	16/30 (53.3)
Cachexia	
MCASCO screening tool	15/27 (55.5)[$]
Fearon criteria	17/30 (56.7)
MCASCO, with Fearon used in placed if MCASCO missing	17/30 (56.7)

[$]One or more participants unable to complete screening tool due to missing data (declined or unable to complete measure)

Table 30 presents the breakdown of scores by screening tool for group one. SARC-F is presented as part of the EWGSOP2 criteria, with those who were confirmed as sarcopenic using the EWGSOP2 algorithm also noted; with 76.5% of those diagnosed with sarcopenia using the SARC-F screening tool also diagnosed as sarcopenic using the EWGSOP2. For cachexia, 55.5% were identified as moderately or severely cachexia. It is noted that the range of scores for the MCASCO tool overlaps between the 'not cachexic' and 'moderate' groups. Scores are provided based upon the answer to screening questions within the MCASCO, however, a diagnosis of cachexia is not provided unless a threshold of 10% weight loss is met, therefore patients may score highly, but remain 'not cachexic'.

Table 30: Malnutrition, sarcopenia, and cachexia scores, using the 3-MinNS, SARC-F, and MCASCO screening tools for group one

Screening tool	**Scores, Mean, SD, Range**	**Scoring category/threshold**	**n (%)**
Malnutrition tool 3-MinNS	Mean: 3.8 (2.6) Range: 0 – 9	No risk: 0 – 2	12/30 (40.0)
		Moderate: 3 – 4	5/30 (16.6)
		Severe: 5 – 9	13/30 (43.3)
Sarcopenia tool SARC-F	Mean 4.9 (3.0) Range: 0 – 10	Not sarcopenic: 0 – 3	10/30 (33.3)
		Sarcopenia: 4 – 10	20/30 (66.7)
		EWGSOP2 confirmed with hand-grip[$]	13/17 (76.5)
Cachexia tool MCASCO	Mean 44.1 (SD 16.2) Range: 17 – 78	Not cachexic*: 17 – 43	12/27 (44.5)
		Mild*	0/27 (0)
		Moderate*: 34 – 44	5 /27(18.5)
		Severe*: 47 – 78	10/27 (37.0)

[$]Due to sample size, and missing data for BIA and TUG, the severity of sarcopenia was not able to be assessed, instead 'probable' sarcopenia, which is enough to trigger intervention in clinical practice, was calculated.

*No defined threshold provided for each category, instead a range of scores are presented

This section investigates the overlap of diagnoses of malnutrition, sarcopenia, and cachexia, using the 3-MinNS nutrition screening tool, EWGSOP2 sarcopenia criteria, and MCASCO cachexia screening tool, for group one. As can be seen in Tables **31a** to **33**, of those (13/30) identified as severely malnourished, n=12 (92.3%) were also identified as cachexic. In contrast, of those identified as cachexic (17/30), only 12 (70.6%) were also identified as severely malnourished.

When looking at those identified as moderately or severely malnourished, of those (18/30) identified as malnourished n=16 (88.9%) were also identified as cachexic, and of those who were identified as cachexic (17/30), n=16 (94.1%) were identified as malnourished.

Of those who were identified as severely malnourished (13/30), n=8 (61.5%) were diagnosed as sarcopenic, and of those who were identified as sarcopenic (16/30), n=8 (50%) were identified as severely malnourished. Finally, of those who were identified as cachexic, (17/3), 9 were diagnosed as sarcopenic (52.9%), of those who were diagnosed as sarcopenic (n= 16), n=9 were diagnosed as cachexic (56.2%).

No statistically significant relationships were seen between malnutrition and sarcopenia (OR 1.8 [95% CI:0.41 – 7.81] p=0.433), or between sarcopenia and cachexia (OR 0.96 [95% CI: 0.23 – 4.10], p=0.961). A statistically significant overlap was seen between severe malnutrition and cachexia (OR 28.8 [95% CI:2.91 – 284.76], p=0.004). When including moderate and severe risk of malnutrition, this relationship remained significant (OR: 88 [95% CI:7.08 – 1094], p=>0.000).

Table 31a: Cross-tabulation of malnutrition and cachexia diagnoses, according to the 3-MinNS (severe risk) and MCASCO tools, with Venn diagram to illustrate

	MCASCO*		
3-MinNS	+ve	-ve	
+ve	12	1	13
-ve	5	12	17
	17	13	30

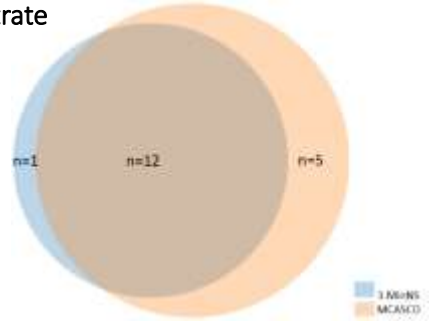


Table 31b: Cross-tabulation of malnutrition and cachexia diagnoses, according to the 3-MinNS (moderate risk and above) and MCASCO tools, with Venn diagram to illustrate

	MCASCO*		
3-MinNS	+ve	-ve	
+ve	16	2	18
-ve	1	11	12
	17	13	30

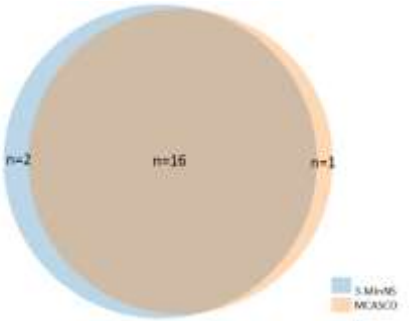


Table 32: Cross-tabulation of (severe) malnutrition and sarcopenia diagnoses, according to the 3-MinNS and EWGSOP2 tools, with Venn diagram to illustrate

	EWGSOP2*		
3-MinNS	+ve	-ve	
+ve	8	5	13
-ve	8	9	17
	16	14	30

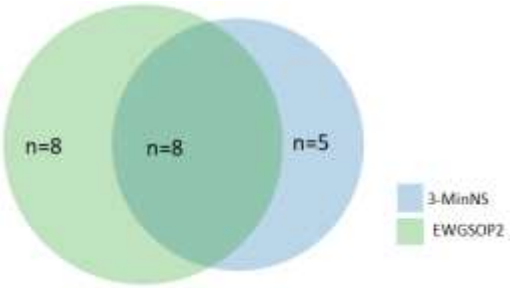
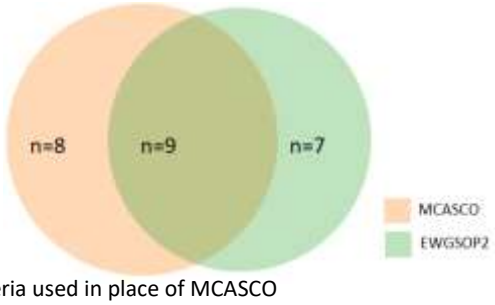


Table 33: Cross-tabulation of malnutrition and cachexia diagnoses, according to the EWGSOP2 and MCASCO tools, with Venn diagram to illustrate

	EWGSOP2*		
MCASCO*	+ve	-ve	
+ve	9	8	17
-ve	7	6	13
	16	14	30



*For missing data, SARC-F used in place of EWGSOP, and Fearon criteria used in place of MCASCO

Tables 34 and 35 outline the overlap between malnutrition screening tools. As seen in **Table 34** of those identified as at risk of severe malnutrition by 3-MinNS (11/30), 8 (72.7%) were identified as at high risk of malnutrition by MUST. Of those identified as not at risk of malnutrition by 3-MinNS, (16/30), n=3 (18.8%) were identified as being at risk by MUST, with a correlation coefficient of 0.486.

As shown in **Table 35**, of those identified as at risk of malnutrition by 3-MinNS (13/30), 10 (76.7%) were identified as at risk of malnutrition by PG-SGA. Of those identified as not at severe risk of malnutrition by 3-MinNS (17/30), 3 (17.6%) were identified as being at severe risk by PG-SGA (17.6%), with a correlation coefficient of 0.593.

Table 34: Overlap between MUST and 3-MinNS malnutrition screening tools

	MUST (high risk)		
3-MinNS (severe)	+ve	-ve	
+ve	8	4	12
-ve	3	13	16
	11	17	28

Table 35: Overlap between PG-SGA and 3-MinNS malnutrition screening tools

	PG-SGA (severe)		
3-MinNS (severe)	+ve	-ve	
+ve	10	3	13
-ve	3	14	17
	13	17	30

Table 36 outlines the overlap between sarcopenia screening tools. Of those who were predicted to be sarcopenic by the SARC-F (20/30), n=13 (65%), were confirmed as having probable sarcopenia by the EWGSOP2 criteria. Of the n=7 who were not, n=4 had adequate grip-strength measures, and n=3 declined or were unable to complete the hand-grip strength measures, or chair stand test, therefore were excluded from results. Correlation coefficient 0.739.

Table 36: Overlap of sarcopenia screening tools

	EWGSOP2		
SARC-F	+ve	-ve	
+ve	13	4	17
-ve	0	10	10
	13	14	27

Of those who were identified as cachexic by the MCASCO (17/30), n=16 (94.1%) were also identified as cachexic following the Fearon, 2011 criteria (**Table 37**). Of those who were identified as cachexic following the Fearon criteria (17/30), n=16 (94.1%) were also identified as cachexic following the MCASCO screening tool. Correlation coefficient 0.929.

Table 37: Overlap of cachexia screening tools

	Fearon		
MCASCO	+ve	-ve	
+ve	16	1	17
-ve	1	12	13
	17	13	30

Table 38 tabulates the overlap of (moderate or severe) malnutrition, sarcopenia and cachexia. In total, 83.3% of participants in group one were identified as having at least one of the three conditions, of which, 26.7% were identified as having one of the conditions, 56.7% with two or more, and 30.0% were identified as having all three conditions. **Figure 16** illustrates the overlap of each of the three conditions.

Table 38: Overlap and combinations of diagnoses of (moderate or severe) malnutrition, sarcopenia, and cachexia

Combination of diagnoses of malnutrition, sarcopenia, and cachexia	**Presence of diagnosis by individual category n %**	**Presence of diagnosis by combined categories n %**	**Presence of any diagnosis n %**
Three diagnoses present			
Malnutrition, sarcopenia, and cachexia	9 (30.0)	9 (30.0)	
Two diagnoses present			
Malnutrition and sarcopenia	1 (3.3)	8 (26.7)	25 (83.3)
Malnutrition and cachexia	7 (23.3)		
Sarcopenia and cachexia	0 (0.0)		
One diagnosis present			
Malnutrition only	1 (3.3)	8 (26.7)	
Sarcopenia only	6 (20)		
Cachexia only	1 (3.3)		
No condition identified			
No malnutrition, sarcopenia, or cachexia	5 (16.6)	5 (16.6)	5 (16.6)

Correlation coefficients between 3-MinNS, EWGSOP2 and MCASCO scores were calculated. A moderate positive correlation was seen between moderate or severe malnutrition diagnoses and a cachexia diagnosis (correlation 0.796). No relationships were seen between sarcopenia and malnutrition (correlation 0.055) or sarcopenia and cachexia (-0.009).

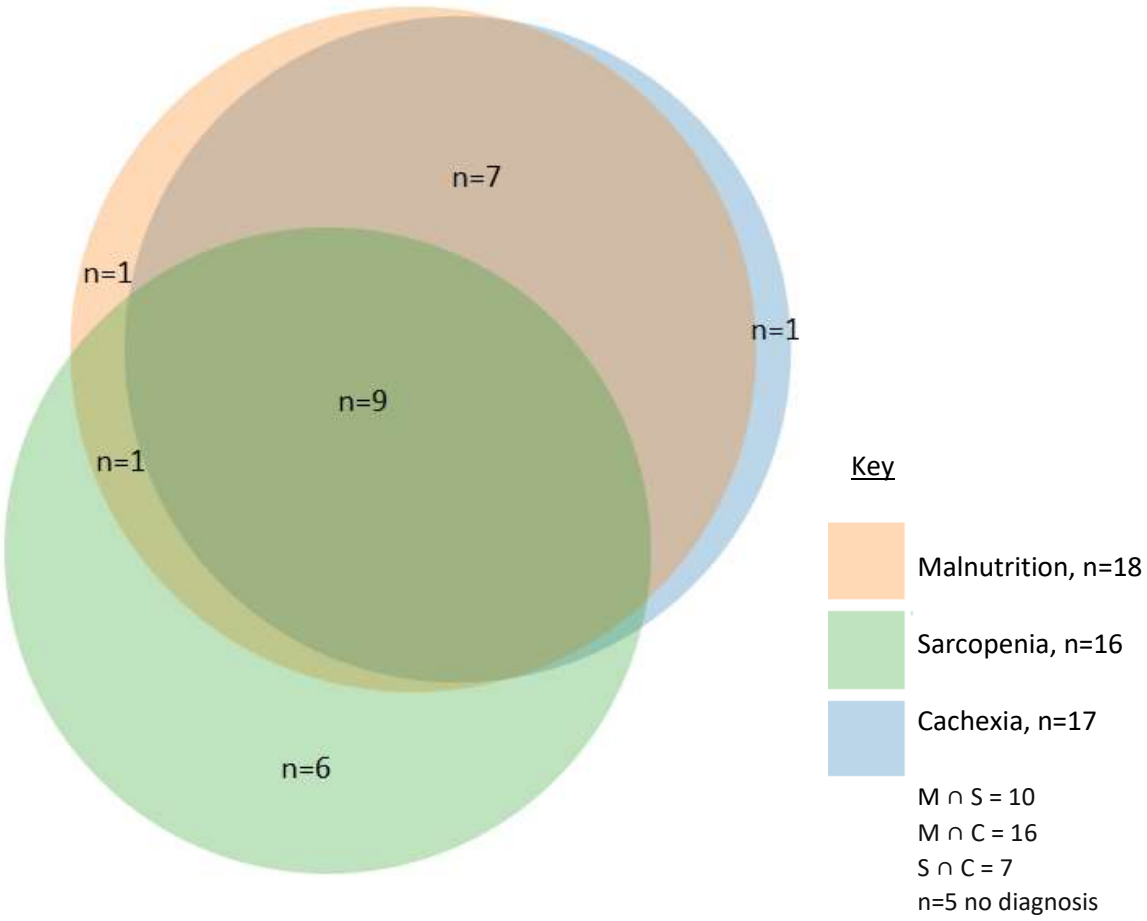


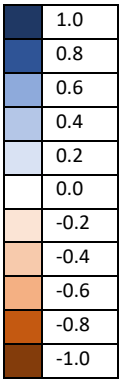
Figure 16: Venn diagram of the overlap of malnutrition, sarcopenia, and cachexia in group one

7.1.4 RQ4: What is the association between malnutrition, sarcopenia, and cachexia, and key clinical characteristics, in this group of older adults with cancer?

Relationships between key baseline characteristics are presented in **Table 39**. A strong positive relationship was seen between; BMI and midarm circumference (correlation 0.785), and Charlson score and chair stand test (correlation 0.788). Moderate positive relationships were seen between timed up and go and skeletal muscle index (Correlation 0.628), and Rockwood score and Timed up and go (correlation 0.697).

Table 39: Correlation coefficients matrix between baseline characteristics

	BMI	MAC	TUG	CST	SMI	HGS	Rock	Charl
BMI	1.00							
MAC	0.785	1.00						
TUG	0.543	0.771	1.00					
CST	-0.190	-0.174	-0.197	1.00				
SMI	0.921	0.700	0.628	-0.309	1.00			
HGS	0.093	0.411	0.443	0.571	0.115	1.00		
Rock	0.049	-0.124	0.697	-0.287	-0.097	-0.362	1.00	
Charl	0.148	0.235	0.023	0.788	-0.120	-0.056	0.294	1.00



Key: BMI: Body mass index, MAC: Mid-arm circumference, TUG: Timed up and go, CST: Chair stand test, SMI: Skeletal muscle index, HGS: Hand grip strength, Rockwood: Rock clinical frailty score, Charl: Charlson comorbidity index

The overlap between the key diagnostic criteria, and the diagnosis of each of the three conditions was also investigated. Of the 30 participants, n=14 reported ≥5% weight loss. Of those with ≥5% weight loss, n=13 (93%) were diagnosed with moderate or severe malnutrition, n=14 (100%) were diagnosed with cachexia, and n=7 (50%) were diagnosed with sarcopenia.

Pearson correlation coefficients between malnutrition, sarcopenia, and cachexia and the predictors seen in **Table 40** were calculated. A strong positive correlation was seen between cachexia and overall weight loss (correlation 0.746). Moderate positive correlations were seen between malnutrition and sunken temples (correlation 0.605), sarcopenia and Rockwood score (correlation 0.680), and cachexia and percentage monthly weight loss (correlation 0.664). A moderate negative correlation was also seen between malnutrition and BMI (correlation -0.614) and malnutrition and percentage meal consumption (correlation -0.665).

Table 40 displays odds ratios from univariate logistic regression analysis, of variables predicting each of the three conditions. When predicting malnutrition, body mass index is a statistically significant predictor (OR 0.78, [95% CI: 0.61 – 0.98], p=0.04) in univariate analysis. This means that, as body mass index increases by one unit, the odds of being diagnosed as severely malnourished reduce by approximately 22%. Additionally, percentage meal consumption (OR 2.28 [95% CI: 1.24 – 4.19], p=0.008), appetite (OR: 2.21 [95% CI: 1.16 – 4.20], p=0.015), and

sunken temples were also statistically significant predictors of malnutrition in univariate analysis. However, following a Bonferroni correction for multiple testing, only sunken temples (p=0.04) remained significant.

When predicting sarcopenia, both hand-grip strength (OR 0.75 [95% CI: 0.60 – 0.94], p=0.015), with an approximate 25% decrease odds for every 1kg increase in hand-grip strength, and Rockwood score (OR 2.94 [95% CI: 1.26 – 6.89] p=0.013) were statistically significant predictors in univariate analysis, but did not remain significant following Bonferroni correction.

For cachexia, both appetite (OR: 1.85 [95% CI: 1.01 – 3.39], p=0.048) and percentage monthly weight loss (OR 8.71 [95% CI:1.87 – 40.60] p=0.006), were significant predictors in univariate analysis, with percentage monthly weight loss remaining significant (p=0.05) after multiple correction.

Table 40: Univariate logistic regression of candidate predictors of key patient characteristics

Predictor variable	**Odds ratio**	**95% confidence intervals**	**p-value**	**Multiple correction (Bonferroni)**
Severe Malnutrition				
Hand-grip strength	0.96	0.86 – 1.06	p=0.416	NS
Body mass index	0.78	0.61 – 0.98	p=0.039	p=0.31
Percentage meal consumption	2.28	1.24 – 4.19	p=0.008	P=0.06
Appetite	2.21	1.16 – 4.20	p=0.015	p=0.12
Sunken temples	8.43	1.9 – 37.3	p=0.005	P=0.04
Sarcopenia				
Hand-grip strength	0.75	0.60 – 0.94	p=0.015	p=0.12
Rockwood	2.94	1.26 – 6.89	p=0.013	p=0.10
Cachexia				
Appetite	1.85	1.01 – 3.39	p=0.048	p=0.38
Percentage monthly weight loss	8.71	1.87 – 40.60	p=0.006	p=0.05

7.2 Summary

In this chapter, the quantitative results of the mixed-methods study have been presented. These results indicate feasibility of recruitment and screening for malnutrition, sarcopenia, and cachexia in a group of older adults with cancer. A high prevalence and overlap of the three conditions are seen, with suggested predictor variables to distinguish between, or more rapidly detect the three conditions, also identified, which include: percentage meal consumption and sunken temples for malnutrition, Rockwood frailty score for sarcopenia, and percentage monthly weight loss for cachexia. Results also show a statistically significant overlap between identification of malnutrition and cachexia, with low to moderate correlation of identification of malnutrition seen between malnutrition screening tools.

In the next chapter, **Chapter Eight**, I will present the qualitative interview findings from the mixed-methods study, with synthesis of the quantitative and qualitative components of the study in **Chapter Nine**.

Chapter 8: Mixed-Methods Study: Qualitative results

Mixed-Methods Study: Quantitative results presented the quantitative findings of the mixed-methods study. This chapter presents the results of the qualitative interviews.

Qualitative research questions

Overarching research question:

- What are the experiences and views of older adults with cancer regarding screening for malnutrition, sarcopenia, and cachexia?

Research questions:

RQ5: What are patients' views and experiences regarding assessments for malnutrition, sarcopenia, and cachexia?

RQ6: What are patients' views of the role of, and understanding of, malnutrition, sarcopenia, and cachexia in cancer?

Research objectives:

- To explore and understand patients' experiences and views of the clinical assessment and management of malnutrition, sarcopenia, and cachexia

A topic guide was followed to ensure interview consistency, see **Appendix 12**, however, the guide was modified iteratively as the interviews progressed. All patient participants who completed the quantitative measures were invited to participate in qualitative interviews. Thematic analysis, whilst viewing the data from a phenomenological perspective, was used to analyse the data. Data collection and data analysis methods are presented in **Chapter Six**.

8.1.1 Participant demographics

Eight participants took part in qualitative interviews; n=2 (16%) female, mean age 75.5 (SD 3.8), majority oesophageal primary (n=4), then breast (n=2), prostate (n=1) and lung (n=1). n=5 participants were diagnosed as malnourished, n=4 as sarcopenic, and n=4 as cachexic. All who were diagnosed as cachexic were also diagnosed as malnourished. n=2 participants were sarcopenic only. One participant was diagnosed with all three conditions.

8.2 Qualitative results findings

8.2.1 Summary of themes

During the process of coding and thematic analysis, four major themes were generated from the data. Major themes and subthemes are presented in **Table 41,** with a brief synopsis presented below.

Theme One: Dissonance

A misalignment, or disagreement, in participants' beliefs, and contradictions in their views and opinions regarding the role, and impact of, malnutrition, sarcopenia, and cachexia, were seen. With participants expressing discrepancies in views of the impact of these conditions upon a macro (population) level, compared to a micro (personal) level. These conflicting beliefs were also seen despite participants reporting experiences of the three conditions, with views misaligning with participants' lived experiences. A contributing factor to this dissonance was a misunderstanding of the three conditions; both their terminology and their role in health, which then also impacted upon their perception of risk of developing the three conditions.

<u>Understanding of malnutrition, sarcopenia, and cachexia</u>

The terms 'sarcopenia', and 'cachexia', were unheard of by participants. Understanding of 'malnutrition' was limited, with perceptions ranging from a serious condition that happened to other people, or a minor ailment with can be easily fixed. Management of these conditions was considered to be 'common sense'. A discrepancy in the importance of nutrition versus function was seen, with participants more motivated to receive interventions or advice to improve their mobility and strength. However, barriers to change were expressed and included a lack of encouragement, ill health, or fear of causing harm.

<u>Perception of risk</u>

Participants' perceptions of their risk of developing problems with their eating, weight, or physical function were influenced by a number of factors, including confidence in perceived positive past health behaviours seen as protective against the risk of developing problems, and alignment with common public health messages. Contradictory views regarding expected deteriorations in nutrition and function were readily expressed, alongside reports of the negative impacts of these three conditions on health and quality of life, showing a detachment in participants self-view of these conditions.

Theme Two: Diagnostic overshadowing

The emotional, physical, and mental burdens of cancer, its treatments, and its side effects, resulted in issues with nutrition, weight loss, and physical function being downplayed or disregarded, by both patients and by clinicians. If concerns were raised by participants, disregard of nutrition and physical function by clinicians perpetuated this belief.

Overlooked and underplayed

Weight loss, and problems with eating or physical function, were often misattributed to other comorbidities, or accepted as a normal part of the cancer process, or ageing, and therefore were not seen as concerning. This lack of concern was perceived by participants to be echoed by clinicians, which reinforced participants' beliefs that nutritional or functional concerns were not 'medical problems'. This reinforced views that the cancer and its treatments were prioritised, with any problems with nutrition or function routinely discounted.

Theme Three: 'Between a rock and a hard place'

Problems with nutrition and physical function remained overlooked until weight loss became visible to others, was rapid, or problems impacted upon cancer treatment options. This then resulted in distress. Participants faced several challenges in raising concerns, including; i) difficulty knowing what, when, and with whom to raise concerns, ii) difficulties having concerns heard, or iii) fear preventing the problem from being raised. This resulted in participants either having to self-advocate for treatment, or becoming resigned to poor health. This resulted in patients being placed 'between a rock and a hard place', with nowhere to turn to address nutritional or function problems.

Theme Four: Study screening for malnutrition, sarcopenia, and cachexia

Screening is seen as 'acceptable'. Moreover, screening was viewed as a positive intervention by some; as an opportunity to raise concerns, or consider any nutritional or functional issues not previously noted, and could be seen as a gateway to help. Some who did not report any expected benefit from screening perceived themselves as not being at risk of these conditions. Screening presented a possible solution to participants who were trapped 'between a rock and a hard place', with screening allowing participants to express concerns, and seek advice. However, screening in routine clinical practice was often not conducted, or acted upon.

Table 41: Main themes, sub-themes and data codes

Main themes	Sub-themes	Original Sub-theme data codes
Theme One: **Dissonance**	**Understanding of malnutrition, sarcopenia, and cachexia**	
	Lay understanding of malnutrition, sarcopenia, and cachexia (macro)	Definition of malnutrition, Definition of function, Terms too technical, Misunderstood terms.
	Detachment of self-view	Do not see own nutrition problem despite significant clinical problems, View of eating habits, View of strength, Disconnect
	Impact of malnutrition, sarcopenia, cachexia (macro) noticeable	Negative effects of malnutrition, sarcopenia, and cachexia – quality of life, Negative effects of malnutrition, sarcopenia, and cachexia – strength and function
	Expected management	Diet not part of cancer treatment, Expectations and views of management of malnutrition, sarcopenia, and cachexia, Common sense
	Function as a priority	Reduced function a problem, ADLs affected by reduced strength, Feels would benefit from Physiotherapy, Interaction of diet and energy seen, Willing to listen to Physiotherapists/Experts, Benefit of function, Completing ADLs, Nutrition low priority
	Motivators to, and barriers for change	Motivators: Keen to improve function/physical activity, Weight loss/strength affecting treatment options Barriers: No Physiotherapy/mobility advice given, Too unwell for advice, Historically well do not need input, No encouragement from clinicians
	Perceptions of risk	
	Confidence in past health	Historically fit/strong cannot have problems, Surprise at weakness, Strength taken for granted, Can fight back
	Unhelpful generic advice	Generic nutrition advice given, ‘Good nutrition’ seen as ‘healthy’, Generic physical activity advice
	Contradictory inevitabilities	Old age means poor function, Weakness with ageing, Expect to rely on family as age, Mobility aids compensating, Reduced diet/weight with age, Reduced strength/function with age, Weight loss expected part of cancer, Weight loss not a concern

	Opposing macro and micro views of nutrition and weight loss	Weight loss as a problem, Nutrition essential to live, Link between diet and treatment, Cannot have weight problem if energy fine, Diet not important in cancer treatment, Optimism bias
Theme Two: **Diagnostic overshadowing**	Overlooked and underplayed: cancer and treatment as priority	Always comes back to cancer, Alternate reasons for weight loss, small weight losses not concerning/attributed elsewhere
	Always comes back to the cancer	Difficulty keeping conversation on nutrition/away from diagnosis, Nutrition side-lined, cancer is overwhelming/frightening
	Nutrition and function disregarded by clinicians	Not a medical problem, Weight loss not picked up or acted on, Nutrition not a concern until affects medical treatment, Function/weight not raised, Difficult to raise concerns
	Explaining unexplained weight loss	Anticancer treatment main cause of reduced energy, Expect low energy, Alternate reasons for low energy/strength
	Not a medical problem	Supportive care, not a medical issue
Theme Three: **Between a rock and a hard place**	Weight loss noted	Family prompting weight concerns, weight loss at diagnosis, Rapid weight loss, Visual weight loss
	Rapid and visual weight loss	Rapid and Visual, Requires visual change to be a concern, Rapid vs slower weight loss, Weight loss at diagnosis
	Difficulties raising and talking about weight loss	Weight loss is upsetting, Difficult to convince self of problem, Difficulties raising concerns, Patient having to advocate for treatment/raise concerns about weight, Dietitians as advocates
	Inevitability of weight loss/poor function (acceptance)	Resigned, Stoic attitude to reduced diet/strength
	Screening as an outlet	Benefit to mental health to discuss nutrition problems, Opportunity to express concern
Theme Four: **Study screening**	Benefits from screening assessment	Motivating to complete physical measures, Screening as an intervention, Screening is acceptable
	Screening issues	Poor recall of measures, Unconcerned about screening as no perceived risk

8.2.2 Theme One: Dissonance

Contradictory views and opinions regarding the role of, and impact of, malnutrition, sarcopenia, and cachexia was reported by participants. This included conflicting beliefs that despite their lived experiences, they would not be affected by poor nutrition or functional problems. Past behaviours and diets were also seen as providing a protective effect against poor nutrition and physical function problems. This was despite participants readily expressing and accepting that other factors, such as ageing, and cancer treatments, would inevitably cause problems with their nutrition and physical function.

> *Luckily for me I was I was very strong to start with… yea… my legs are the weakest, er ya luckily I was strong when all of this hit me so hopefully I can fight back some way (Pt7)*

> *Because I've always been really energetic… I've probably, I've got a lot of stamina, I've had a lot of stamina, I wouldn't say I was fit or anything, I've had a lot of stamina and been able to keep going, and as I say it got to one point in October, erm, when I could just get out of a chair, getting up, getting showered, getting dressed, wiped me out for the rest of the day (Pt1)*

Contributing factors to this dissonance included; i) a misunderstanding of malnutrition, sarcopenia, and cachexia, of both their terminology, and their impact and role in health, and ii) a low perception of personal risk due to confidence in past health behaviours, and a lack of knowledge regarding the aetiology of the three conditions. These factors are discussed:

8.2.2.1 Understanding of malnutrition, sarcopenia, and cachexia

The terms 'malnutrition', 'sarcopenia', and 'cachexia', were poorly understood by participants, with participants not having heard of the terms 'sarcopenia', and 'cachexia' in particular. These terms were described as 'too technical', and were perceived as confusing and unclear.

> *No, not heard of that (sarcopenia) before (Pt1)*

> *Q: …the second one is sarcopenia?*
> *A: Ooph…*
> *Q: Have you heard of it?*
> *A: No (Pt4)*

> *Q: …it's the word cachexia*
> *A: No, nah you've missed me again (pt5)*

Understanding of the term 'malnutrition' was also limited, and was perceived as either a serious condition related to starvation, but more commonly was viewed as conditions only

seen in low-income countries, or as a minor ailment, which would be easily treated or addressed.

> *Well malnutrition I do know what that means, that means undernourished, yeah undernourished, er, another word for malnutrition probably is, intake of food, sufficient intake of food, I don't know how else to describe that (Pt4)*

> *I know that (malnutrition) means – I feel like it [laugh], yeah, that's when you're getting a bit too hungry (Pt5)*

> *I think it would mean to me, in terms of, I think you most hear it in terms of Africa, Yemen and what have you, so a diet that isn't hasn't got all of the necessary sort of parts to it, so being deprived of something in that, and actually, having enough to eat to keep your body ticking over, it would be like that (Pt1)*

The 'technicality' of these terms was often highlighted, to the point of being compared to a complex drug name, which presented a barrier to participants' understanding and willingness to engage.

> *Haven't got a clue. Far too technical (Pt5)*

> *(when asked about 'malnutrition')… very often in hospital, the nurses in particular talk to each other in a medical term, one of the worst things probably, it's not their fault, because I don't know the names of the drugs, but they'll say this drug or that drug, they'll discuss drugs in front of me and you don't know what they are talking about, they do have the edge on you there. If you don't understand something you feel a little bit inadequate (Pt4)*

Other terms, such as 'poor nutrition', were more readily understood, but were still considered to be a minor problem.

> *Oh now, well, weight loss (Pt8)*

> *You know if you're not looking so perky, maybe having er, sort of flu, you know that flu or er, silly little ailments like that over a period of time you think oh there's something along there (Pt8)*

> *Well it er, it's a case of er not, not eating sufficient amount or er, the type of er, food etcetera that you need to, to keep yourself fit (Pt7)*

> *Well, poor nutrition, would mean, not having enough to eat, and the things that don't that are not going to be protein or whatever, er, to keep you going really (Pt2)*

> *That is giving up, it it's lack of appetite, lack of, lack of motivation, you know you, you don't want to be, you just don't want to know about that (Pt8)*

I've heard of that yes. Not a nice word that (Pt 8)

'Good nutrition', and participants' perceptions regarding the most appropriate diet during cancer treatment, was perceived as being 'healthy', eating 'well', and following generic healthy eating messages, such as cutting down on red meat, increasing vegetables, and reducing high-calorie foods.

I had a good diet before, but I do think a lot of the stuff is, erm, the youngsters eat sort of rubbish, which is rubbish anyway (Pt3)

We've always had skimmed milk, hah, as that's more healthy (Pt2)

'The term 'function' was also more readily understood, but still resulted in a wide range of definitions.

Bodily functions? You mean toileting and that sort of thing? (Pt8)

Normal routine actions, in your everyday work, everyday operations really, yeah (Pt8)

Q: how you would describe your, your strength, your function at the moment? A: Quite intelligent, outgoing, thoughtful, I don't ponder things, I just think about things occasionally, but generally speaking I think I'm an intelligent sort of a guy (Pt8)

When relating the impact of these commonly accepted terms (function, poor nutrition), to health, the negative impacts of these conditions was more readily reported. In particular, the negative effects participants were currently experiencing from poor function on their ability to complete activities of daily living, or upon their quality of life, were highlighted.

Getting showered, getting dressed, wiped me out for the rest of the day, and you know, it was just, or we planned to go somewhere and you know I would just, say I couldn't come! (Pt1)

Yes, my strength was yea, was the word I keep using to myself really, (sigh), everyday things that you take for granted you just either couldn't do or such an effort (cough) er, I mean at my worst, before the hospital, it was taking me half an hour to get dressed, you know, put my trousers on, have a lie down, put my shirt on, have a lie, I couldn't believe it, how weak I was really (Pt2)

I don't think I had the energy to deal with other people, as well as meself (Pt3)

This also included the negative effects of these conditions upon quality of life, with nutritional problems affecting participants mood, body image, and enjoyment of food.

I suppose that's what keeps me doing, at the end of the tunnel, I think that, to sit back and think that you're gonna have soup for the rest of your life wouldn't be too good (Pt5)

I don't know where it goes but I've lost a lot of weight, all the weight, all the meat off my thighs and my bottom, ma arms are like spindles (Pt4)

I've er probably got a bit fed up of, certainly when I was on the liquid diet, I don't want to see soup again, er, that was pretty fed-up-ey (Pt2)

Physical function, its association with the ability to complete daily tasks, see family, and its relationship with the ability to tolerate and receive anticancer treatments were readily reported by participants, with improving physical function seen as a high priority. Participants were motivated to make lifestyle changes to improve their physical activity.

I feel I am gradually getting better every day, and er, trying to challenge myself to walk a bit further every day (Pt2)

What I'm aiming for is, at [Hospital] I have to pass, and I can't remember the name of it, but I call it a fitness test, and the results go to the consultant who's supposed to do the surgery, and that will decide if I am fit enough to have the operation. So that is what I am aiming for (Pt1)

You need physiotherapy, you need work, you need to muscle to move again, cos if you don't do that you stiffen up, and that makes it worse, so that's what I want, I want – Action (Pt8)

However, the association between their personal nutrition and function was not reported. Despite acknowledging the wider relationship between diet and function – this was often not applied to their personal health.

You are gonna lose your strength cos you're not eating the proper stuff, as such, you're getting your nutritions and stuff, but I don't think, its, you could do better… [laugh] so I think er you know losing your weight you lose your strength (Pt5)

Well obviously, you wouldn't have had as much energy to fight, and it think that's important that you need to keep as fit as you can (Pt3)

With only those who were receiving treatment for their nutritional problems recognising the impact of improving dietary intake on energy and function.

I'm obviously well not taking in a whole, a proper amount of calories, but certainly more than I was and my portions are bigger than they were. And my energy levels are improving, I can get past teatime, were yeah before even lunchtime, sometimes I would sleep the afternoon away (Pt1)

External causes, such as poor sleep, or the effects of anticancer treatment, were often cited as the cause of reduced energy levels.

> *I don't get any sleep on a night… you know… I was really, very fortunate last night because I managed to get an hour's sleep, erm, I haven't got the strength to do anything, you know (Pt6)*

> *I thought I was quite a very fit strong person, but the chemo doesn't really like me, doesn't like the chemo very well, so (Pt3)*

This included when nutritional supplements were prescribed by consultants, perceptions were that these were primarily to improve physical function, not nutrition.

> *It's too risky to do the operation if you're not fit enough, erm, t, er, s, he's er, er he's prescribed… fortisip, fortisip compact … I did see him then, it was only shortly before, they recognised that I needed building up (Pt2)*

However, although participants reported the significant impact of these problems upon their health, a poor understanding of nutritional and functional problems often meant that their treatment and management was perceived as easy, with many participants reporting their management as 'common sense'.

> *I have to say, some of it is common sense, about your eating, etcetera (Pt2)*

> *No no, a bit like common sense really. Don't keep still and you've got to keep moving (Pt2)*

> *People'll come in and say right so this, do that exercise, do that ten times, once you've started to do that you'll find that the muscle strength will start to come back again, and you'll be able to say well I can stand a bit more (Pt8)*

With the conditions themselves viewed by some as having little importance in relation to cancer treatment.

> *…and I don't honestly think, er, diet plays a bigger part of it really, but that's just my opinion (Pt3)*

For most, a disconnect was seen with malnutrition when viewed as a personal problem, compared to a wider issue, with many participants, including those who had significant issues with their nutrition, viewing nutritional problems as unrelated to their health, or as something that would never happen to them, despite prior acknowledgement of the severity of these conditions to others and themselves.

A: So I suppose that's about it really. It's not, it's not something that I take seriously, because it's not going to happen to me. Yeah. Q: Can I ask you why it (weight loss) might not happen to you? A: Because I'm going to make the best of what I've got, I I've every intentions of bouncing back (Pt8)

There were exceptions to this, with some participants acknowledging the relationship between nutrition and function, but this was again often not applied to themselves.

Make sure you eat as nutritionally as you can, which will help you feel better, and cope with the treatment better. I think that's a bit of common sense… I don't honestly think, er, diet plays a bigger part of it really, but that's just my opinion. (Pt3)

Despite the improvement of physical function reported as a key priority for many participants, several barriers to change were expressed. These included; a lack of encouragement from health care staff, a lack of advice provided, and an associated fear of causing more harm than good, and being too unwell or unreceptive to advice at the time. A few participants were self-motivated to improve their function.

But it's good having the advice [pause] rather than thinking about it, thinking am I gonna make things worse you know leaping up and down or whatever (Pt5)

During the days of my stay on the ward, I was took by my own initiative to walk, just up the corridor … But nobody said oh keep doing that (Pt2)

Somebody tried to, they came in and tried to but I think at that time I wasn't very receptive anyway (Pt4)

An additional barrier, of self-assurance in their perceived current strength due to past health, was also expressed.

Yes I'm quite strong yeah, I've upper body strength is very good, always has been, erm, the only bad thing is the blooming inability to do things (Pt8)

Yeah my strength isn't as good as it used to be, but luckily for me I was I was very strong to start with… yea… my legs are the weakest, er ya luckily I was strong when all of this hit me so hopefully I can fight back some way (Pt7)

8.2.2.2 Perception of risk

Participants' perceptions of their risk of developing problems with their eating, weight, or function were influenced by a number of factors. This included participants understanding of these problems, which was often poor, unrealistic optimism regarding the risk of development of these conditions, and an assumed ease of treatment.

I mean luckily I can eat, so I won't ever get, er, malnutrition type of thing, but er, if it got worse, then you would (Pt5)

To eat a satisfactory meal I would presume, is all, all I would like, yeah (Pt7)

Well, posh meal somewhere, or, or something like that, anything just to perk things up a bit (Pt8)

Additionally, confidence in past health behaviours, and how they aligned with key public health messages, often reassured participants that they had a low risk of developing nutrition problems, or gave confidence in their ability to 'fight back' or improve.

Er, no cos I'm a very good eater, or I was (Pt8)

No, not really, as, as I think I've told you, I was, big, pretty fit, so.. erm, didn't go into it about… (Pt7)

You know it is important to keep, erm eating as healthy as you can. But I did before so it were not hard for me. I must admit I don't eat as much meat as I used to do, I aren't a meat lover anyway I don't particularly…I ate it because I probably did it but I, if I don't want it I don't want it. I always have a lot of fruit and veg, and things like that so, it hasn't been hard for me at all. I haven't altered my eating habit (pt3)

Nutrition wise I think I'm quite healthy living, so, obviously there are certain things I have altered a bit, you know I don't eat so much sweet stuff (Pt3)

These views were held despite prior acknowledgement by participants of the negative impacts that poor nutrition, weight loss and poor function have had on their health.

Well okay, it's affecting me as far as I can't eat anything solid, or anything with bits in, like a tin of vegetable soup, I couldn't eat that, unless I mashed it up, then I could eat it, so obviously I'm not having like my full English type of thing! So, I miss out on all the food, because I'm basically living on just soup, so I'm having soup twice a day, and me, me forti, fortisips, er and that's basically what I live on (Pt5)

This disclosed a disconnect between participants' view of the personal impact of these conditions, compared to their population-level views, and betrayed a confidence and optimism bias. These views were expressed by many, despite some having personal experiences of all three conditions. This showed a detachment between their personal beliefs regarding their risk of developing either poor nutrition or problems with their mobility or function, and their wider beliefs of the impact of these conditions in general.

This difference in perceived risk, expected ease of treatment, and confidence in past health behaviours was betrayed when some participants went on to experience nutritional or functional difficulties, with participants expressing surprise when they had difficulty recovering from them.

> *In the normal process of an accident in the home you usually just dust yourself off and go at it again don't you? Well that didn't happen you see, somebody had to come and pick me up, and I was in a heck of a state (Pt8)*

> *I couldn't even walk to the shops, or around the shop and I found that quite difficult because I think well if you don't use it, well, you're gonna lose it aren't you? And I do still find, er, difficulty doing things that I didn't think twice of doing before. I get quite out of breath doing things (Pt3)*

Participants also reported a conflicting view of surprise if their eating or function either did not deteriorate whilst receiving anticancer treatments, or if their nutrition or function improved.

> *I expected to lose a bit o' weight, but I lost very little (Pt3)*

> *But I got my appetite back! Which is, a good thing (Pt2)*

8.2.3 Theme Two: Diagnostic overshadowing

The emotional, physical, and mental burdens of cancer, its treatments, and its side effects, resulted in issues with nutrition, weight loss, and physical function being downplayed or disregarded by patients, and being perceived as also disregarded by clinicians.

Problems with nutrition, weight, or function were often attributed to other health conditions, or accepted as a normal aspect of a cancer diagnosis, or cancer care. The overshadowing cancer diagnosis and its treatments were routinely scapegoated as the cause of each of these problems, and as they were 'expected', they could therefore be easily be discounted.

> *So on the last chemo on that day I also had radiotherapy as well, the next day I was absolutely jiggered, you know, absolutely, and I just spent most of the day in bed (Pt4)*

> *I expected at some point the cancer would cause me to lose weight, but I mean we also expected that the chemo, that might be a side effect of the chemo as well, erm (Pt1)*

> *When I get home I'm quite tired, but that's only to be expected (Pt2)*

The immensity of the cancer diagnosis, and its impact upon multiple domains of participants lives, resulted in cancer taking over conversations, and meant other problems paled in comparison, and were therefore not addressed.

> *The other thing I thought of the other day is really sometimes it's as though cancer is your first thought about everything, and I thought there's life beyond that, it doesn't seem to be going along with it, treatment, erm, you know coming along in the car I said you know that's all we've talked about, we're an hour away from here, about treatment and what the futures going to hold (Pt8)*

> *Q: is there anything about your weight, or your strength, or function, or eating, that we maybe don't pick up on as well as we should do, that we could have asked you about?*
> *A: No, not really no, I think [laugh], there are other things to worry about at the time (Pt7)*

This included addressing nutritional or functional problems, with participants reporting difficulty concentrating on other aspects of their health.

> *Right, yeah, I can understand that. Being told you've got cancer, er… when I was sat there, all I could see was a noose, I'd had it, he'd ended my life, I was doomed, I was going to die, that's what you see when you're told you've got cancer, cos cancer is what kill ya (Pt4)*

Problems with nutrition or function were often framed in their relation to the participant's medical diagnosis, and ability to manage this; with one participant more concerned about their ability to swallow tablets, rather than being able to eat.

> *Oh absolutely, at that stage eating was a no-no, I couldn't ever swallow tablets, so that caused a furore as they had to find liquid tablets, erm... tablets, all my tablets had to be transformed to liquid, and some of the tablets they do not make in liquid, so I had to go without them (Pt4)*

Attributing weight loss, or other problems, to their cancer, or other previous medical issues, further solidified participants' views that these were not important problems. Negative health outcomes were always attributed to the participant's cancer diagnosis or treatment, with other aspects of their health, such as recent weight loss or poor appetite, overshadowed.

> *You're gonna you know weaken off type of thing. I think that's possibly so much of the problem as well, erm then possibly the chemo on the top (Pt5)*

> *I don't think that was because, er, of the cancer, I think it was because of the treatment, and it made it difficult to cope (Pt3)*

This was further solidified when concerns were perceived as continuously ignored by clinicians, despite multiple attempts by participants to raise their anxieties.

> *Basically I told him [consultant] again, about the eating where the problem was, as I tell most people! [laugh] so I think everybody must know (Pt5)*

8.2.3.1 Overlooked and underplayed

In addition to the cancer, weight loss, or problems with eating or physical function, were also often misattributed to other health conditions, or were considered to be part of the normal ageing process. These factors meant participants often dismissed these issues.

> *Something was going wrong with my throat, so, [WIFE] wasn't surprised as she'd said for a little while you're always coughing and bringing up mucus there's something wrong, and I said there's not cos I have COPD and it's probably from that (Pt4)*

> *Well that, well that's inevitable really, I think everybody eventually succumbs to that process (ageing) (Pt8)*

This lack of concern regarding weight loss, or functional problems was echoed by clinicians. If raised by participants, problems were often dismissed by the medical team as a normal part of cancer and its treatment. This compounded participants' beliefs that these issues were not medical priorities, or considered part of their medical treatment, and were therefore insignificant problems.

> *No, because I think the macmillan nurses are very good at sort of helping you with the care of yourself as a person, whereas the doctors are more concerned with the treatment (Pt3)*

> *The first time… when we did raise it (weight loss) in discussion it was more or less attributed to the chemo… (Pt1)*

However, participants reported that they were often not asked about their nutrition, or their physical function, and were not provided with advice by the medical team, further solidifying beliefs that these problems were not 'medical' concerns.

> *Er, no, nobody mentioned weight loss at all (Pt7)*

> *Q: On the strength side of things, did you ever raise it to anybody, or did anybody ever raise it with you? A: No, Not at all (Pt5)*

> *Q: Have you seen anyone about your strength – the physiotherapists? When you've been in hospital, to help you with your mobility or walking about? A: No, no I haven't no (Pt6)*

For those participants where the medical team did mention physical activity or nutrition, this was often viewed as unhelpful, with participants encouraged to continue with 'healthy' diets, or participants were provided with untailored, generic nutrition and physical activity advice during their treatments.

> *Just keep as normal as you had before but make sure you eat as nutritionally as you can, which will help you feel better, an' cope with the treatment better (Pt3)*

> *They all said don't go things like swimming or spas or cruises, or that but other than that keep life as normal (Pt3)*

> *Yeah, they have said well try and do as much as you can, when you can (Pt3)*

> *Well I think mainly they told you what not to eat [e.g., neutropenic diet], rather than what to eat, er things like shellfish, erm, and a love me prawns, that was quite difficult for me, erm, I mean they give you a list don't they? (Pt3)*

Weight loss in particular was easily overlooked and underplayed, with participants themselves often justifying unexplained weight loss on other issues; other comorbidities, stress, and ageing.

> *Something was going wrong with my throat, so, [WIFE] wasn't surprised as she'd said for a little while you're always coughing and bringing up mucous there's something wrong, and I said there's not cos I have COPD and it's probably from that (Pt4)*

> *I may have lost a pound or two with the stress and strain, but I don't think so, no (Pt8)*

This ability to attribute weight loss to common causes confirmed to participants that these problems were minor, and therefore would be simple and easy to treat.

> *You're losing a bit of weight, you need to be eating something, that sort of thing, it wouldn't worry me, we'd just do something about it, yeah (Pt8)*

Indeed, deteriorations in function or nutrition were often perceived as normal, with expected deteriorations due to ageing, the effects of anticancer treatments, or excess body weight, reported by participants.

> *Well that, well that's inevitable really, I think everybody eventually succumbs to that process (ageing) (Pt8)*

> *I finished chemotherapy, end of December, and got an infection… both of those things combined, really wiped me out, er, really struggling to walk from room to room, er, (cough) which was not a surprise (Pt2)*

Probably a lot of people carry a bit more weight than they normally do, can't move as quick-quickly as they used to do (Pt8)

I expected at some point the cancer would cause me to lose weight, but I mean we also expected that the chemo, that might be a side effect of the chemo as well (pt1)

You retire and you slow down and as you slow down you don't use your arms so much and obviously your muscles aren't as strong as they were because you're not using them and like anything if you don't use your muscles, you're gonna you know weaken off type of thing (Pt5)

With participants compensating for these, for example with the use of mobility aids, or reducing daily activities.

Yeah, I think it is something that is a progression, you you've got to do that (use walking stick), yes, you're, you're compensating for your growing old aren't you? (Pt8)

We planned to go somewhere and you know I would just, say I couldn't come! You know, we ended up, doing, not doing a lot of things were [HUSBAND] went off… and did them… or, I'd really, really sort of have to manage… …we'd planned the day… so that I could maybe, do thirds of a day, so maybe I'd do the morning, and rest in the afternoon (Pt1)

These aspects combined resulted in poor nutrition and problems with physical function being overlooked and underplayed by both participants and their clinicians, strengthening views that cancer treatments are prioritised, with any problems with nutrition or function routinely attributed to this, and therefore seen as an accepted, expected, and unconcerning parts of cancer care.

8.2.4 Theme Three: Between a rock and a hard place

Problems with nutrition and function often remained overlooked by patients until crucial indicators that caused concern or distress occurred, such as family commenting upon visible weight loss, weight loss being rapid, or problems with nutrition and physical function which impacted upon cancer treatment options.

Erm and then I only noticed, you [HUSBAND] said that I was getting thinner, and then all of a sudden, I noticed, and when you notice yourself that you are… (Pt1)

I think it was when other people started to mentioning it, how thin I was getting, that opened my eyes a little bit, you know, erm (Pt6)

And several days not eating anything I'd actually lost 2 stone, so I was living off me body weight, and every everybody was saying how ill I was, and I bloody felt ill (Pt4)

When I was in hospital the time before last he came to see me when he discharged me and erm he said then that he doesn't think I'd be strong enough for chemo… because unfortunately although I'm eating I don't seem to be putting weight on, and erm, he said it's a little bit too savage, this chemo, so they're gonna try maybe radiography (Pt6)

I would try and hold it in the 8 stones… cos I started at nine stone three, and, and then this seven started appearing, and I'm thinking this really isn't good news, you know… (Pt1)

The visual changes in particular, in both physical appearances, and reducing portion sizes, were a strong prompt for concern.

I could no longer eat the volume of food… that I was eating… I sort of when down for my dinner to a salad plate, and then to a tea plate, erm, and, and I, I knew when I had to stop (Pt1)

Well, the, the weight, losing weight was erm, er, I don't, I don't really know, about it at all, it was a surprise to me, I mean, I realise when, when things like, well the biggest thing that prompted me was when my wedding ring fell off, and, ha, I thought that's a bit strange [laugh], so we went through weight loss and things like that, and measuring, and realising that I had lost quite, quite a bit of weight (Pt7)

With participants expecting family or close friends to prompt, or express concern, based upon their physical appearance.

No, what I think would happen there, somebody would say, [WIFE], or, you're losing a bit of weight, you need to be eating something, that sort of thing (Pt8)

This was compared to small or slow weight loss, or decline in function or mobility, which were often overlooked, and not seen as concerning.

Q: Have you noticed any change in your weight recently? A: I may have lost a pound or two with the stress and strain, but I don't think so… I haven't any worries, eating habits or anything like that (Pt8)

However, once the weight loss did become a concern, participants experienced difficulties with both raising these concerns, and having them taken seriously by clinicians.

I suppose between end of September through to… beginning of this year when I felt a little frustrated because we raised these issues… and we… were… not fobbed-off that's too strong a word, but nothing really materialised… (Pt1)

Along with difficulties in accessing primary care clinicians, participants believed that weight loss was not taken seriously unless it was visibly seen by their general practitioner (GP). They felt weight loss concerns were not listened to, as weight loss or functional problems were attributed to other conditions, or seen as normal.

But you see the problem is you can't go in to see your GP to really explain it or show him how you're losing weight, so I suppose he's at a disadvantage (Pt5)

If you say to somebody, you've lost two stone, I mean, it's just a word, but if you see somebody, and they've lost two stone, you can see the difference, so, then you maybe would have sussed it out a lot quicker maybe… (Pt5)

This resulted in participants experiencing frustration, both with health care professionals, and with the consequences of the weight loss.

The only frustration was this weight loss, lack of energy started to arise, just getting somebody to take it onboard which has now happened (Pt1)

Well I think if erm, they'd have picked up erm the problem earlier that would have helped things yeah (Pt5)

Further difficulties were reported by participants in raising their concerns, with participants delaying or avoiding raising concerns, due to fear, or weight loss not being seen by themselves an indicator of a health problem.

I didn't, I didn't realise how much I was losing, and how quickly… it didn't, it didn't strike me at first, and then I realised, then ai thought you know this is too much, I've got to do something an I went to the doctors and… then all this I was diagnosed. And what you… It was diff, it was hard to come to an convince myself… (Pt6)

Well the weight loss, didn't prompt me oh, in fact erm, it's very very strange because I erm I was diagnosed with prostate cancer I didn't have any symptoms or common symptoms, related to it… I had no idea I had, or could have had. So, so could, the only thing was er, I er I had er (prostate cancer), I had the what was it, the weight loss, that was one of the things, an the other was er pain around the back (Pt7).

This conflict placed participants in a difficult position – when recognising the seriousness of the situation, but being unable to access help, and having nowhere to turn. Participants found themselves between a rock and a hard place, of being concerned regarding their weight loss,

eating or physical function, and noting the negative effects of these conditions, but being unable to seek help, or have their concerns acknowledged.

This meant participants had to self-advocate for treatment, with many continuing to raise their concerns about their weight or eating, as they were never asked.

> *Er (pause) er, no (pause). Anything to do with nutrition has come from us (Pt1)*

> *I think I told them (Pt4)*

> *I think it was just a question of persuading somebody that, er I thought the weight loss was quite dramatic… (Pt1)*

Some participants took their own initiative to increase their mobility when they did not receive advice.

> *Erm… (pause) not on the wards, er no… I think during the days of my stay on the ward, I was took by my own initiative to walk, just up the corridor (laugh) (Pt2)*

However, many became resigned, and accepted their poor health, with participants expressing a stoic attitude to their nutrition and function problems, with the belief that their nutritional or functional problems could not improve.

> *Resigned? You can't help but be resigned, I mean, I can't do the things that I used to do now, I'm reconciled to it, what I do say though is that I'll make the best of what I've got left (Pt8)*

> *Erm (pause) I'm a bit pragmatic about things really, that's what's gonna work, so that's what I'll do, you know, so yeah, that's much the same now, erm I'm embracing this pureed diet because you know, it's fine (Pt1)*

> *No problems I kinda've got used to the idea, it's like having headache, you get used to it after a while! (Pt5)*

> *Well it's alright, it just realise that I can't eat as much as I could (Pt7)*

> *Ah, well I, my er, well my nutrition has deteriorated, er, as, I came off the chemotherapy, and the er, the steroids, and things like that, and er that has, that has made my appetite… poor, which I am adjusting to (Pt7)*

8.2.5 Theme Four: Study screening for malnutrition, sarcopenia, and cachexia

The process of screening for malnutrition, sarcopenia, and cachexia during this study was seen as acceptable by all participants, but recall of screening measures, and questions in particular, were poor.

> *I don't sort of find it intrusive, I don't find it you know, sort of difficult (Pt1)*

> *I don't see the problem with anybody really, I mean it's not anything too personal, is it? The questions (Pt5)*

> *Erm… questions you asked… [paused] erm, not just off hand, nah, you'll have to help me out with that one (Pt5)*

> *Vaguely, vaguely remember something about it yeah… (Pt7)*

> *I didn't mind at all, I though, you know, fair enough I don't mind any questions (Pt4)*

Exceptions to these included measures of physical function, e.g., hand grip strength, sit-to-stand, which were more frequently recalled.

> *We did yeah, I squeezed a machine, I jumped up and down out of a chair, and I swung from one chandelier from the other and I was Rambo (Pt4)*

> *I remember we had to sit in a chair and stand up,… you know, so many times (Pt2)*

Although screening was seen as acceptable, some participants did not perceive any benefit from screening due to beliefs that they were functionally and nutritionally well, particularly if they had strong confidence in their past health, and its protective effects.

> *I wouldn't be too bothered, but I wouldn't mind if they wanted to do it (screening) yeah (Pt7)*

But for some, screening was seen as a positive intervention; as it provided an opportunity to raise concerns, or consider any nutrition or function issues that may have not been considered before.

> *I think in a way, it was at the back of my mind, and that's why that, that sitting down and standing up, brought it, if you like, to my mind (Pt2)*

Several benefits of completing screening were reported: i) a positive opportunity to discuss nutrition and eating, as participants did not know what was relevant to raise/ask about their nutrition or function with their medical team, or had not considered their nutrition or function

before, with screening providing an opportunity to think about these issues, ii) reassurance that they could complete simple measures of function e.g., sit-to-stand; participants had been hesitant to mobilise due to fear of causing harm or falling, and the presence of a health care worker to supervise provided confidence, and iii) beneficial to mental health, of sharing their concerns. This suggests screening could be seen as an intervention in itself.

> *Sometimes it, it is harder to know what is relevant, for, from my point of view as to what you find relevant, you know (Pt1)*

> *Well the fact that I could do it, cos you know I was thinking, you know to be honest I could get out of bed and just about get to the bathroom, and er and I thought that was it, and to do that and I thought, maybe I could do a bit more than that, you know? So I was quite surprised that I could do that. Me son actually came and said he didn't think he could do it! (Pt2)*

> *(It) helps if you're talking about it… it's better than it kind of left in the dark and only me knowing (Pt5)*

> *Well, motivated and gave a bit of a boost really. Well all I can say is that you coming and doing those really helped me, quite a bit (Pt2)*

8.3 Feedback loop analysis of qualitative findings

Following thematic analysis, it was possible to identify a number of feedback loops. See section 3.5.2.5 for the methodology and core process steps for conducting loop analysis. See **Figure 17** for the feedback loop diagram.

Loop one: Impact of misunderstanding

A lack of knowledge by participants regarding malnutrition, sarcopenia, and cachexia, and their causes and consequences, affected perceptions of the risk of developing these problems. The assumed impact of the conditions on personal health was often minimised. This was despite acknowledgement that nutritional and functional problems may cause negative effects in others e.g., poorer health, reduced quality of life. This low perception of risk continued, despite nutritional and functional problems being viewed as a normal part of the cancer journey, and an expected part of ageing - this exposed a dissonance in participants' beliefs regarding nutrition and physical function, fuelled by a misunderstanding of the aetiology and potential severity of these conditions.

Loop two: Ending in a rock and a hard place

A low risk perception of developing these conditions was also contributed to by diagnostic overshadowing – with clinicians perceived as downplaying or disregarding any concerns participants had regarding their nutrition or physical function. This included attributing such issues e.g., weight loss, to the cancer, and seeing them as an expected and therefore normal part of cancer treatment. This disregard of symptoms confirmed to participants that these issues were minor, and therefore posed little risk to their health. Further, unexplained weight loss, or reduced physical function, was easily attributed to other health problems, and therefore not seen as concerning. This was further contributed to when participants received inadequate or unhelpful 'generic' nutrition or physical activity advice, which cemented a belief that past positive health behaviours e.g., following a 'healthy' diet, or staying 'active', were protective against any future nutrition or functional problems. Finally, the emotional, physical and mental burdens which resulted from a cancer diagnosis meant that nutritional and/or physical function problems were not prioritised by participants.

Combined, this overshadowing of nutritional and physical function problems, with the dissonance participants experienced regarding their assumptions about their risk of developing these conditions, caused conflict when participants eventually became concerned with the impact of these problems; particularly when rapid weight loss, or poor physical function, endangered their chances of receiving anticancer treatments. This left participants at an impasse; with nowhere to turn to have their concerns addressed.

Loop three: The role of screening for malnutrition, sarcopenia, and cachexia

The assessments for these conditions, completed as part of this study, were seen as acceptable. Moreover, screening presented an opportunity for participants to consider and raise any concerns that they had regarding their nutrition or physical function, in an environment where their concerns would not be disregarded. Screening could also be seen as an intervention in itself, with physical tests of function reassuring participants that they were able to complete basic movements. This showed that screening could act as an opportunity to positively affect each aspect of the loop diagram; with screening providing an opportunity to educate patients on the risks of these conditions, provide an outlet for those in a rock and a hard place, and prevent diagnostic overshadowing, as concerns regarding nutrition and physical function would be actively sought out and addressed. However, participant receptiveness to advice can be affected by participant self-belief in their current health; with confidence in past health behaviours and attributes preventing participants from believing screening is required.

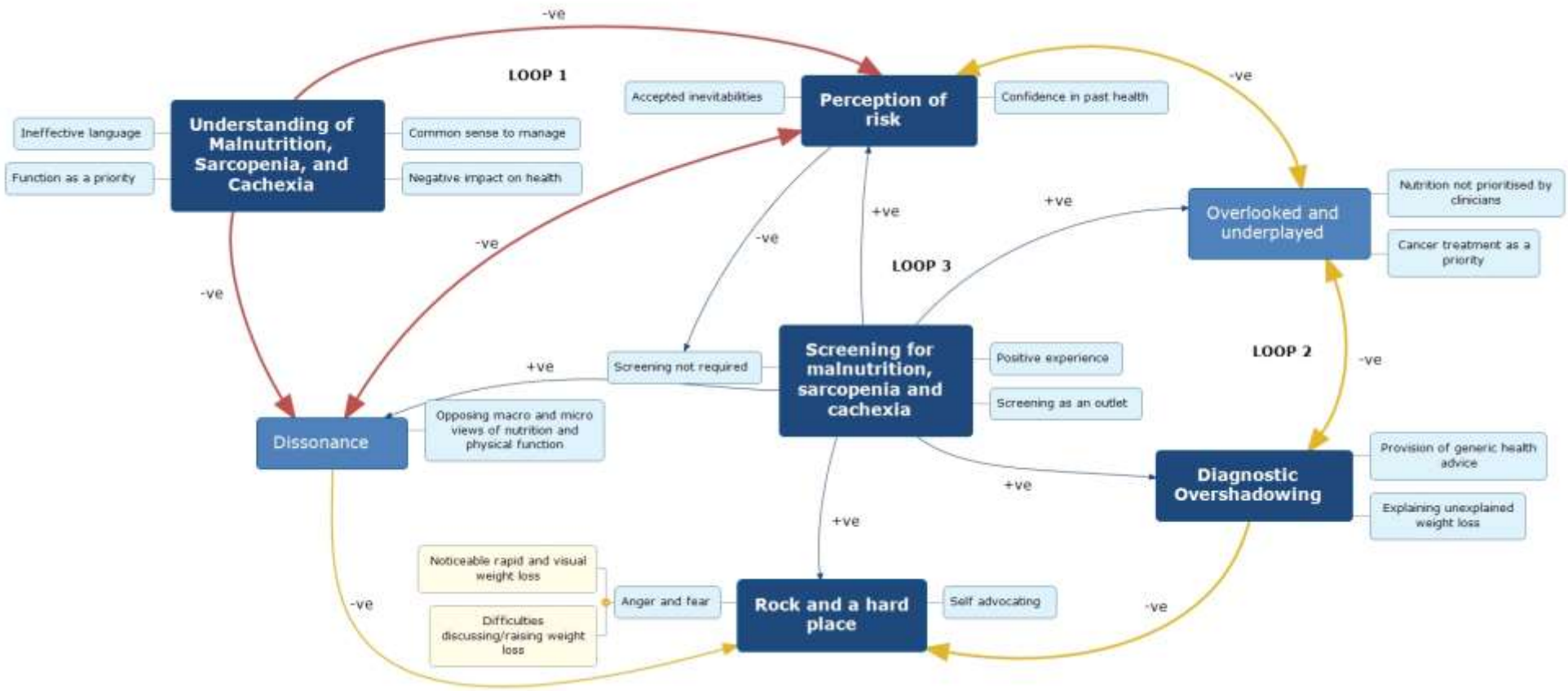


Figure 17: Feedback loop diagram illustrating interlinking themes of the views and experiences of malnutrition, sarcopenia, and cachexia in older adults with cancer

8.3.1 Feedback loop analysis summary

The feedback loop diagram, **Figure 17**, provides an illustrated map of the relationships between themes, and the positive and negative feedback loops which have influenced patients' views and experiences of malnutrition, sarcopenia, and cachexia. This figure details the three loops generated from the qualitative thematic analysis, of; i) impact of misunderstanding, ii) ending in a 'rock and a hard place', and iii) the role of screening for malnutrition, sarcopenia, and cachexia, and how they interlink.

Loop 1 illustrates the impact of the lack of understanding of the three conditions; of a misunderstanding of the causes and consequences of these conditions. This loop negatively impacts upon each of the associated themes (perceptions of risk, dissonance), which, alongside the impact of diagnostic overshadowing (loop 2) – both by patients and clinicians, terminates in patients being trapped between 'a rock and a hard place'.

Sufficient disregarding, or downplaying, of these conditions and their symptoms, caused by a lack of knowledge, both by patients and clinicians, also demonstrates the negative impact the lack of knowledge – of both patients and clinicians – has on patients' experiences. These negative feedback loops culminate when visual changes of the internal problem of cancer, become external, and visible to patients themselves and their family members. At this point, patients are placed at an impasse: of experiencing fear or concern regarding negative physical changes, e.g., rapid weight loss, but having no avenue through which to have this addressed (loop 2).

However, screening for malnutrition, sarcopenia, and cachexia presented a possible solution to this (loop 3). Screening provides an opportunity for patients to express their concerns in an environment where concerns regarding nutrition or physical function are acknowledged, and are subsequently addressed. Screening may also provide an opportunity to address patient's knowledge gap regarding the impact of the three conditions, which in turn may alter their perception of their risk, and challenge the dissonance experienced of seeing nutritional and functional problems as expected and accepted parts of ageing, cancer, or other comorbidities. Loop 3, screening, also reduces the risk of these conditions being overlooked and underplayed, by actively recognising nutritional and physical function problems, and providing the avenue needed for these issues to be addressed.

8.5 Summary

In this chapter, the findings of the qualitative interviews from the mixed-methods study have been presented. Thematic analysis through a phenomenological lens of eight semi-structured interviews, investigating patients' views and experiences of malnutrition, sarcopenia, and cachexia, led to the generation of four themes; i) dissonance ii) diagnostic overshadowing, iii) between a rock and a hard place, and iv) study screening for malnutrition, sarcopenia, and cachexia. Results of the thematic analysis were then employed in feedback loop analysis to investigate the relationships between themes. Three distinct loops of; i) impact of misunderstanding, ii) ending in a 'rock and a hard place', and iii) the role of screening for malnutrition, sarcopenia, and cachexia were generated. From this, feedback loop analysis, investigating the relationships between themes, was conducted, generating three distinct loops of; i) impact of misunderstanding, ii) ending in a 'rock and a hard place', and iii) the role of screening for malnutrition, sarcopenia, and cachexia, and how they interlink.

In the next chapter, **Chapter Nine**, I will synthesise the findings from this chapter and **Chapter Seven**, and discuss the integrated findings of the mixed-methods study.

Chapter 9: Mixed-Methods Study: Synthesis of Results

In the previous chapters, **Chapter Seven** and **Chapter Eight**, the results of the mixed-methods study were presented. In this chapter, a modified critical interpretive synthesis and discussion of the qualitative and quantitative aspects of the study are presented. This synthesis will address the feasibility of recruitment, the prevalence, overlap, and patient understanding of malnutrition, sarcopenia, and cachexia, and the role of screening for malnutrition, sarcopenia, and cachexia.

9.1 Modified critical interpretive synthesis of mixed-methods results

A modified critical interpretive synthesis was completed to synthesise the results of these quantitative and qualitative aspects of the mixed-methods study. See section **3.6** for a discussion of the use of a modified critical interpretive synthesis. For the mixed-methods study results, each research question is presented against summaries of the collected quantitative and qualitative data, see **Table 42**, with a further synthesis of the results presented in section **9.2**. A discussion of these synthesised results, in addition to the results of the systematic reviews (**Chapter Four** and **Chapter Five**). in addition to a discussion of the thesis' overall aim, are presented in **Chapter Ten**.

Table 42: Modified critical interpretive synthesis of quantitative and qualitative results

Research questions	Quantitative results	Qualitative results	Synthesis of quantitative and qualitative results addressing RQ
RQ1: Is it feasible to recruit and screen a group of older adults with cancer for malnutrition, sarcopenia and cachexia?	▪ Invite to consent ratio: 3:1 ▪ Minimal missing data on screening questions (0.55%) ▪ High levels of missing data for physical function measures (69.2% missing timed up and go test) ▪ Higher completion of measures not requiring mobilisation (e.g., hand-grip 87.2% completion, mid-arm circumference 92.3% completion) ▪ Missing screening measures due to inability/declination to complete measures	▪ Screening is seen as a positive experience; an opportunity to consider and address previously overlooked issues ▪ Positive beliefs regarding own health and belief in past health behaviours can present a barrier to screening ▪ Benefits to completing physical screening measures reported: - Reassurance of ability to complete basic physical movements, with completion of measures reported as motivational; encouraged increased physical activity	It is feasible to recruit and conduct the study screening measures for all three weight-losing conditions. Minimal missing data, apart from physical function tests requiring mobilisation; fear of harm or assumed inability to complete affecting uptake of measures.
RQ2: What are the demographics and clinical characteristics of this group of older adults with cancer?	▪ n=39, male=72.2%, age 75.6yrs (SD 4.2) ▪ Cancer diagnoses: 35.9% upper gastrointestinal, 28.2% lung, 12.8% breast, 10.3% prostate, 7.7% colorectal, 5.1% head and beck ▪ 59% localised, 41% metastatic cancer ▪ 3:1 recruitment rate in hospitalised patients ▪ Disproportionate recruitment of localised cancers vs metastatic cancers ▪ Pandemic affected available population sample ▪ >87.2% recent biochemical markers – feasible to collect without additional testing	▪ Subgroup of n=39 ▪ n=8, male=75%, age 75.5 (SD 3.8)	It is possible to recruit older adults with a range of ages, sexes, and cancer types and stages, without study-specific biochemical testing, however, the study population representativeness was affected by the COVID-19 pandemic (reduced ambulant outpatient recruitment, reduced inpatient numbers and sicker admitted patients)
RQ3: What is the prevalence and overlap between	▪ 43.3% severe malnutrition (60% moderate or severe malnutrition) ▪ 56.7% cachexic	▪ Association between nutrition and function not recognised at an individual level by participants	There is substantial overlap between conditions clinically, but not recognised by participants.

malnutrition, sarcopenia, and cachexia, in this group of older adults with cancer?	▪ 53.3% sarcopenic ▪ 83.3% evidence of ≥1 condition, 30% evidence of all three conditions ▪ 94.1% with evidence of cachexia also had evidence of malnutrition ▪ 50% of severely malnourished patients with evidence of sarcopenia ▪ Moderate correlation was seen between diagnosis of malnutrition with 3-MinNS and PG-SGA, poor correlation between 3-MinNS and MUST ▪ 94.1% diagnosed as cachexic with MCASCO also diagnosed with Fearon, 2011 criteria	- Acknowledged when discussing the impact on wider health, but not connected with own cancer journey -Poor self-perception of the relationship between own nutritional state and physical function	There is a high prevalence of malnutrition in particular, yet often overlooked by participants and viewed by participants as downplayed by clinicians. The significance of nutrition in relation to function is not appreciated by patients, but function is valued in relation to its impact on fitness for cancer treatment and quality of life.
RQ4: Association between malnutrition, sarcopenia, and cachexia and key clinical characteristics	▪ Percentage meal consumption and sunken temples associated with malnutrition ▪ Rockwood frailty score associated with sarcopenia ▪ Percentage monthly weight loss associated with cachexia ▪ Skeletal muscle index correlated with BMI (0.9) and measures of physical function (0.7 mid-arm, 0.6 timed up and go)	▪ Malnutrition is viewed by participants as having a limited impact upon cancer treatment ▪ Physical function prioritised, with participants motivated to make changes: - Association with treatment tolerance/ability to receive further treatment - Barriers to screening include timing of interventions, receptivity to advice, fear of harm ▪ Visual changes are important in identifying concern: - Rapid weight loss causing visual changes seen as a red flag - Other visual changes e.g., portion sizes, also prompt concern by patients and their families ▪ Contradictory opinions also seen of decline in physical function not seen as concerning – attributed to ageing and seen as normal	Visual appearance is important in the diagnosis of malnutrition, both physical appearance, and visual appearance of meal portion sizes. Reduced physical function and dietary intake were noted by participants but viewed as a normal part of the ageing/disease process. The link between physical function and nutrition is not recognised by participants, despite the known interdependent relationship.

RQ5: What are patients' views and experiences regarding assessments for malnutrition, sarcopenia, and cachexia?	▪ ≥99% completion rate of screening questions ▪ Missing data was more common for the physical measures, with assumed inability to complete affecting participants' decisions to attempt measures	▪ Benefits to completing physical measures reported: - Motivating to complete measures - Reassurance of ability to complete basic physical movements ▪ Screening is seen as a positive experience; an opportunity to consider and address previously overlooked issues ▪ Positive beliefs regarding own health and belief in past health behaviours can present a barrier to screening	≥99% completion of screening questions infers that assessment of the three conditions is acceptable. There was a discordance in uptake and acceptability of physical measures between quantitative and qualitative findings. High declination of physical measures due to assumed inability to complete; however, if completed, this acted as an intervention to encourage physical activity. Screening presented an opportunity to highlight and address nutritional and physical function problems.
RQ6: What are patients' views of the role of, and understanding of, malnutrition, sarcopenia, and cachexia in cancer?	▪ No findings related to this research question	▪ Terms 'malnutrition', 'sarcopenia', and 'cachexia' are poorly understood ▪ Physical function is seen as a priority, but several barriers to change. ▪ Nutrition is not prioritised and is overshadowed by cancer, seen as easy to treat. ▪ Dissonance is seen in views of personal vs population view of nutrition problems, despite lived experience ▪ Conditions overshadowed: - Low perception of risk of developing conditions - Low priority compared to cancer and treatment - Perceived as overlooked or disregarded by clinicians - Perceived as a normal part of cancer and ageing, therefore accepted and disregarded	A lack of understanding about the three conditions, their causes, consequences, and their relationship with participants' health resulted in a low priority being placed on these problems. A dissonance was seen between the assumed inevitability of the conditions and the low perception of risk of developing the conditions. Patients perceptions were reinforced by the belief that clinicians disregarded nutritional concerns, therefore were not a medical concern, were expected, or were irremediable. Frustration was experienced when disregarded nutritional and physical function problems resulted in significant

		▪ Difficulty addressing nutrition and physical function problems once participants become concerned: - Difficulty acknowledging the problem to self -Weight loss/reduced mobility not recognised as concerning symptom(s) - Frustration in the inability to receive support or have concerns addressed	adversities e.g., impact on ability to tolerate anticancer treatment, with participants having nowhere to turn to for support.

Summary

▪ It is feasible to recruit to a study, and screen, for malnutrition, sarcopenia, and cachexia in hospitalised older adults with cancer

▪ Screening for these conditions is feasible and acceptable in clinical practice and may be streamlined

- Poor uptake of some markers of physical function, but correlation between functional markers and measures of muscle mass e.g., timed up and go and skeletal muscle index, could be used to streamline screening
- Reduced dietary intake, and visual appearance of emaciation, appear to be key predictor variables for malnutrition
- Rapid weight loss is suggested as a key predictor variable for cachexia
- Rockwood frailty scale is suggested as a key predictor variable for sarcopenia
- Visual markers of change are more easily recognised and considered important by patients

▪ Malnutrition, sarcopenia, and cachexia are highly prevalent but overlooked and under-recognised conditions in older adults with cancer. Contributing factors include:

- Misunderstanding of the conditions by patients, and a misconception of their roles in cancer care (Loop one: impact of misunderstanding)
- Perception that these problems are overlooked or downplayed by clinicians, and overshadowed by the cancer diagnosis, with problems considered normal, and as inevitable consequences of cancer treatment and ageing (Loop two: ending in a rock and a hard place)
- Terminology used when discussing conditions needs further consideration to ensure appropriate communication and understanding by patients
- Although physical function is seen as a high priority by patients, the association between nutrition and function is not well known, or acted upon

▪ There is significant overlap in the diagnosis of malnutrition and cachexia, with all three conditions seen in a subset of participants

- 30% of participants had evidence of all three conditions, with 83% with evidence of one or more condition
- Heterogeneity of markers for malnutrition, with homogeneity seen between markers of malnutrition and markers of cachexia, makes differentiating between the two conditions difficult in this population

▪ Screening may be a potential solution to address these conditions and issues (Loop three: The role of screening for malnutrition, sarcopenia, and cachexia)

- Screening provides an opportunity for patients to express concerns, consider the impact of these conditions and impart information on these conditions (particularly the link between nutrition and physical function), and may act as an intervention in itself to improve physical function

The following sections expand upon and discuss the synthesis of results presented in **Table 42**, including the feasibility of recruitment (section **9.2**), feasibility of, and challenges of screening for the three conditions (section **9.3**), and the role of screening for malnutrition, sarcopenia, and cachexia (section **9.4**).

9.2 Feasibility of recruitment

Study recruitment rates were recorded to assess the feasibility of conducting a larger study. During group one, the target recruitment rate was achieved during the first nine weeks, see **Figure 14**. Had recruitment continued at this rate, the target sample size would have been reached within the expected timescale. However, these recruitment rates were not sustained during the COVID-19 pandemic and were reduced further (8:1 recruitment ratio) when only recruiting participants in group three who also consented to involvement in qualitative interviews.

It is important to note that participant recruitment across non-COVID health research was seriously affected by the COVID-19 pandemic, with cancer patients' enrolment in clinical trials falling by 60% in 2020 – 2021 (467). The continuing impact of the COVID-19 pandemic, and increased pressures on the NHS, are likely to continue to affect study recruitment rates, with ongoing interruptions to research and clinical activity, restrictions to movement, and ongoing fears for healthcare facilities (468), affecting health research. As discussed in section **6.7.5**, the COVID-19 pandemic increased the risk of sampling bias, through a reduction in hospital admissions, with only those with the most severe illness admitted, and therefore accessible for study invitation (453).

Discrepancies in the numbers of participants with colorectal cancer included in the study (**Table 26**), compared to the Office for National Statistics data **Table 28**, are noted; with the lower inclusion rate of 7.7% of participants with colorectal cancer, compared to the number of overall hospital admissions for colorectal cancer in England (24.7% admissions). The reverse discrepancy is also seen with upper gastrointestinal cancer admissions, of 35.9% of study participants, compared to 18.6% of admissions in England.

Difficulties in recruiting older adults, and those receiving palliative care are recognised. There is a reduced uptake in study participation of patients with advanced cancer (469-471), with potential participants citing barriers to involvement such as; fatigue, being too unwell, experiencing distress, or having uncontrolled symptoms, such as pain or nausea which prevent involvement (469-471). These were all reasons presented by patients who declined involvement in this study, alongside other reasons such as; a lack of interest in the study topic,

too-high time burden, or fear of missing or delaying inpatient medical reviews with ward clinicians.

This study was designed to be as non-invasive and low burden as possible, due to the planned recruitment of patients with life-limiting illnesses. Careful attention was paid to the study design, information collected from participants (to avoid duplication or requesting information that could be gained from other sources e.g., computer systems), and the consenting process. These included pre-screening of patient demographics (e.g., age, cancer diagnosis), a clear description of study content, including an explanation of the meaningfulness of the research, and flexibility of recruitment (472).

Older adults are often excluded from clinical research studies (473), with exclusion commonly based on morbidity, frailty, or ageism (473), resulting in older adults being an under-represented group in health care research, despite increasing life expectancies and an ageing population (474). Older adults often do not seek out involvement in health research (475), or are deterred by barriers including poor health, fatigue, family resistance to involvement, and limited time to appraise study content (476). Additionally, other studies including older adults often experience higher drop-out rates, and see higher numbers of potential participants being screened to recruit one participant (usually 3:1) (477). However, older adults are more likely to have positive experiences of research, even if the studies result in a neutral or negative outcome; with reasons including a desire to contribute to science, and improve the health of others (478, 479). This was seen within this study, where the limited benefit to the participants involved was explained at the point of recruitment, however, many participants reported a desire to be involved to benefit others who may be in similar positions in the future. The barriers to recruiting participants with metastatic cancer to studies are well documented, and include heavy symptom burdens, severity of illness, family and provider gatekeeping (469, 472), and likely explain some of the discrepancies between actual recruitment and sample week incidences of metastatic disease, namely the disproportionately lower recruitment of those with metastatic cancer, compared to those with localised cancers.

This study was designed to mitigate these aforementioned barriers, and in addition to minimising patient burden, additional time was allotted to be spent with potential participants during the recruitment period, to take time to explain the research, and answer any potential questions. Measures and study questions were also conducted at the participant's chosen speed, with the option to pause, or return, to study measures or questions at a later time or date. Additionally, minimal participant-involved follow-up was planned, due to the potential burden and higher potential attrition rates, with only those who consented to interviews contacted after the completion of study measures.

9.2.1 Outpatients

Outpatient recruitment was attempted from weeks four to nine. Several difficulties were encountered that would need to be addressed in a future study. Difficulties with timings; of approaching potential patient participants whilst waiting for outpatient appointments, or whilst waiting for test results, presented challenges, and no patient participants were recruited directly from outpatients. Outpatient recruitment was suspended at week nine due to the developing situation with COVID-19, with a decision made to focus time on recruiting inpatients to achieve a larger sample before restrictions were imposed. Once the study was re-opened, a change in Trust policy meant that recruiting from outpatients was no longer appropriate, with Trust COVID-19 guidance limiting patient contact and staff/researchers in additional clinical areas. This, alongside a decision to focus upon inpatients where recruitment targets were more likely to be achieved, led to a decision not to recruit further from outpatients.

Obstacles to recruiting patient participants from outpatients have been previously identified and include; a lack of privacy in outpatient clinic settings and fears about confidentiality, concerns about parking, transport and travel, family or work responsibilities, alongside other general anxieties including excessive time commitments to studies, fear of detection of a new health problem, and cost of participation; both financial and non-financial e.g., time, emotional commitment (480). In another study, community-based patients were significantly less likely to be recruited to an observational palliative care study, compared to hospitalised patients (481).

This study did not demonstrate the feasibility of recruiting from an outpatient setting. Alternate methods, such as embedding a researcher in consultant-led clinics, or improved engagement with hospital allied health professionals to aid with recruitment, may have led to improved recruitment rates (472, 480).

9.2.2 Recruitment summary

An overall recruitment rate of 3:1 was seen in the study or groups one and two, suggesting this aspect of recruitment was not affected by the pandemic. However, a reduction in the available numbers of patients, directly caused by the pandemic, meant that recruitment rates slowed dramatically for groups two and three. As COVID-19 is likely to continue to affect recruitment rates to clinical studies, due to limitations on hospital attendance and potential participants' fears regarding COVID-19 risk (453, 468), factors to improve recruitment rates must be considered.

This could include improving recruitment in outpatients, such as by embedding researchers in consultant-led clinics, or allied healthcare professional clinics. The challenges of recruiting patients who are receiving palliative care remain, with mitigation strategies suggested including; avoiding restrictive eligibility criteria, inclusion of 'gatekeepers', such as hospital ward and outpatient staff in the recruitment process where ethical approvals allow, and ensuring an adequate number of researchers for the study, to allow all eligible patients to be approached in a timely manner before discharge home (469, 471).

9.3 Feasibility of, and challenges to, screening for these three conditions

My findings show completion of the 3-MinNS and PG-SGA malnutrition screening tools to be feasible in hospitalised older adults; my study confirms findings that completion of the PG-SGA is feasible in hospitalised adults (482, 483). Little research has been conducted previously regarding the feasibility of completion of the 3-MinNS screening tool in hospitalised adults, with research focused upon the assessment of the tool's prognostic ability, or sensitivity and specificity (178, 179). However, the results of this study suggest feasibility of use of the 3-MinNS screening tool in hospitalised adults (178).

For sarcopenia, the SARC-F screening tool was completed by all participants. The SARC-F comprises the first step of the EWGSOP2 criteria and has been found to have high specificity, but low sensitivity (112, 484). Therefore, the additional components of the EWGSOP2, of hand-grip strength or chair stand test to further assess sarcopenia, with confirmation using BIA, or other measures of muscle quantity or quality, are needed (17). However, the feasibility of completion of the aforementioned additional measures was low (30.8 – 41.7%), see **Table 27,** questioning the feasibility of use of the EWGSOP2 criteria in hospitalised older adults with cancer.

The MCASCO screening tool for cachexia had the greatest number of measures (11). A fundamental feasibility issue of the MCASCO was the requirement for measures of lean body mass and loss of lean body mass over the last 12 months. A decision was made to include BIA due to its comparatively quick and low-burden procedure for assessing muscle quantity compared to other methods such as Computer Tomography (17). However, due to the low uptake of BIA in this study, its use to determine lean muscle loss in hospitalised older adults with cancer may not be the most appropriate method, despite its rapid application and low patient burden.

Four biochemical markers, including the inflammatory marker C-reactive protein, were required for the cachexia screening tool. In this study, blood results had an overall completion rate of 95.5%, with a mean time from collection to performance of study measures of 2.1 days

(range 0 – 11 days). This suggests that the use of routine biochemical markers for hospitalised patients is feasible for the completion of the cachexia screening tool.

These results demonstrate that it is feasible to screen hospitalised older adults with cancer for malnutrition, sarcopenia, and cachexia, using the 3-MinNS, PG-SGA, SARC-F, and Fearon et al., 2011 criteria (19, 109, 141, 178). However, difficulties were encountered when completing the additional physical function measures and measures of muscle mass for the MCASCO (16) and EWGSOP2 2019 (17) criteria, with some declining due to a perceived inability by patients to complete the measures, or a fear of falling.

Positive physical self-perceptions are known to be associated with increased physical activity, and conversely, higher levels of fear of falling are a predictor of activity avoidance or restriction in older adults (485, 486), as well as the risk of future falls (487). Therefore, declining measures of physical function due to fear of falling, or perceived inability to complete the measure may correlate with actual performance, and risk of sarcopenia, or low skeletal muscle mass (485, 486). From this, declining, or an inability to undertake these measures, could be seen as a 'fail' test result, in particular when considering markers of function, which in itself could be considered as a predictor variable (485, 486).

The low completion rates of some of the physical measures support the need to streamline, or limit, the number of measures undertaken to screen for the three conditions. Correlations between the results of functional assessments (**Table 39**) may help streamline screening tools and reduce the need for multiple functional measures to assess muscle quality and quantity. This, therefore, may make implementation or uptake in practice more likely, with results suggesting a relationship between skeletal muscle index and functional markers such as timed up and go. However, further research is required due to the small study sample size. A recent comparison of the chair stand test, timed up and go, and hand-grip against BIA also found correlations between skeletal muscle index and functional measures (e.g., chair stand, grip strength) (488).

Completion of the SARC-F screening tool was higher than that of the EWGSOP2. However, as the SARC-F has low sensitivity, it is not recommended as a stand-alone tool to diagnose sarcopenia (17, 484), with the addition of assessment of muscle strength required to determine probable sarcopenia, which is adequate to recommend treating sarcopenia clinically (17). Both chair stand and grip strength can be used to assess muscle strength. In my study, completion of grip strength was higher than completion of chair stand test (87.2% vs 33.3%), suggesting its use as a first-line measure, over that of chair stand, in hospitalised older adults. Other, less onerous measures, including measures of calf circumference (SARC-CalF), have

been suggested since the commencement of my study (121), which may also reduce patient burden, and may be more feasible in this population. This includes the suggestion of a three-item SARC-F screening tool (116). However, initial assessments of diagnostic accuracy have suggested that the three-item SARC-F may not be suitable for screening for sarcopenia in community-dwelling older adults (116).

In addition to assessments of muscle mass, the MCASCO also uses biomarkers to assess for cachexia. This study indicates the feasibility of using biomarkers to assess cachexia in hospitalised older adults with cancer. Biochemical markers have previously been suggested for use as markers of malnutrition, e.g., the Prognostic Nutritional Index, which in our meta-analysis (**4.5.3.2**), was associated with overall survival (HR: 1.89 [1.03 – 3.48], p=0.04) (221). However, inclusion of markers of inflammation in the diagnosis of malnutrition is complex. Although they can be useful as predictors of prognosis (395), and may indicate increased nutritional requirements (172), as argued previously (section **4.6**), inflammatory markers are not specific to malnutrition, and may feature in the mechanisms for the development of all three conditions (36, 78, 81, 153), but are a key driver in the development of cachexia (489), making their use in the identification of cachexia logical.

In addition to the challenges of differentiating between these conditions, other barriers to addressing the three conditions were also raised in the qualitative interviews. These included: the timing of advice provided, patient illness and receptiveness to advice, patients' fear of causing harm when completing physical activity, belief in protective past health behaviours, and a misunderstanding of the conditions themselves.

Findings of the qualitative interviews also highlighted the benefits of screening for the three conditions, which, alongside screening providing an opportunity to raise and address concerns, screening, and in particular the physical function measures, was also seen by some patient participants as an intervention in itself – with support to complete supervised basic physical function activities (e.g., sit to stand) empowering and providing reassurances regarding their mobility. Factors involved in empowering patients with long-term health conditions have been suggested to include ‘knowledge and confidence in decision making’, and a ‘positive attitude and sense of control’, which relies upon effective communication between patients and health care providers (490). It has been argued that empowering patients and their families and carers about malnutrition, through raising awareness and understanding of the impact of the condition upon health, and encouraging patients to speak up about their nutritional concerns may aid in the detection and treatment of malnutrition, including helping to identify those at risk of malnutrition *before* the visible signs of weight loss are seen (491). However, my interview data showed that, even when patients spoke up about their concerns, they were

disregarded by many clinicians, or concerns about weight loss were attributed to the disease process or ageing, and therefore are inevitable and unmodifiable.

However, screening presented a possible solution to this problem; whereby the topics of nutrition and physical function are raised by a health care professional, are discussed and presented as modifiable or manageable conditions. Screening may also provide reassurance regarding patients' physical abilities, and enable education regarding the impact of nutrition to the prioritised health aspect, of physical function, may provide a fire-break in the cycles shown in **Figure 17: Feedback loop diagram**.

9.3.1 Identifying 'at risk'

Although this study identified predictive variables of the results of the screening tools, it is noted that these potential predictor markers, along with many of the markers used in the screening tools, signify *when* a problem has already occurred. Screening tools for malnutrition aim to identify a 'risk' of developing the condition. An example of this is the MUST screening tool (158), where a score of two or more indicates a 'high risk' of malnutrition developing. However, advice is to 'treat' at this point, when weight loss or low body mass index are already present. Similar is also seen with the 3-MinNS tool (178), with a score of three or greater indicating a patient is 'at nutritional risk', with weight loss >3kg, substantially reduced nutrient intake, or visible muscle wasting is required to score ≥3. These criteria suggest *established* malnutrition, as per consensus definitions (140, 145, 150), rather than a 'risk' of malnutrition, with these tools incorrectly misattributing 'diagnosed' malnutrition for 'risk' of malnutrition.

For sarcopenia and cachexia, each of the tools are designed to detect an established disorder; for the SARC-F (109), a score of 4 or more is 'predictive of sarcopenia and poor outcomes', the EWGSOP2 algorithm (17) confirms 'probable' sarcopenia, and the MCASCO indicates 'mild' 'moderate' or 'severe' cachexia (21).

This problem is emphasised when looking at the psychometric properties of the screening tools, with tools such as the CASCO (long-version of the MCASCO) (54), the 3-MinNS (178) and the SARC-F (109) validated against the consensus definitions of their associated conditions (18). These tools are either picking up established conditions or are incorrectly assessing the 'risk' of a condition developing, as their criteria for risk are mapped against diagnostic criteria for the conditions.

From this, it can be seen that the screening tools are identifying established nutrition-related conditions, of established weight loss, established nutritional concerns, and established functional decline, and in some cases, falsely labelling this as 'risk' of developing the condition, seen with the malnutrition screening tools in particular. Rather than diagnosing the actual risk

of developing the conditions, these screening tools identify *when* a problem has already occurred; when these conditions are already impacting upon patients' abilities to tolerate anticancer treatments (10, 11, 90), or upon their quality of life (41, 93, 163), with late diagnosis of these conditions reducing the available effective treatment options (10, 19, 23, 28).

9.3.2 Prevalence of malnutrition, sarcopenia, and cachexia

The prevalence of the three conditions varied depending on the screening tool or criteria used, see **Table 29.** The prevalence of malnutrition in adults with cancer worldwide is estimated between 25 – 71%, depending on the cancer diagnosis (12), with upper gastrointestinal and lung cancers seeing the highest prevalence (159). As seen in **Table 34** and **Table 35**, there is only a mild to moderate correlation between the results of each of the screening tools. This demonstrates the need for key predictor indicators of malnutrition, and for standard screening criteria, to avoid missed diagnoses of malnutrition in older adults with cancer.

Overall estimates of sarcopenia prevalence in adults with cancer vary depending on the criteria used, but are estimated at an average of 38.6% of older adults with cancer (pre-therapeutic) (77), with upper gastrointestinal and lung cancers again seeing a higher prevalence (77). As my study participants were currently receiving, or had previously received treatment, and the sample included n=12 (40%) upper gastrointestinal or lung cancer patients, levels of sarcopenia were understandably higher (66.7% SARC-F tool, 53.3% EWGSOP2) than the overall estimated prevalence. As the SARC-F screening tool is known to have high specificity but low sensitivity (112), confirmation of diagnosis using the EWGSOP2 screening algorithm (17) was required; explaining the reduced prevalence when using the algorithm.

With cachexia, the estimated prevalence in cancer patients ranges from 11 – 74%, depending on cancer diagnosis (27). As nearly half of my study sample were diagnosed with upper gastrointestinal, lung, and head and neck cancers, it is unsurprising that the prevalence of cachexia in this study is high. High concordance was seen between the MCASCO screening tool and Fearon 2011 criteria (19), with 94.1% diagnosed as cachexic by both methods (correlation coefficient 0.929). However, this is likely explained by the key diagnostic criteria for each being a weight loss of >5% (16, 19). However, the severity of cachexia as indicated by the MCASCO (16) (mild, moderate, severe) could indicate the stage; of pre-cachexic, cachexic, or refractory cachexia, influencing how patients are managed, and would be useful for further detailed assessment, once cachexia is initially identified through the screening.

Although the three conditions are highly prevalent in this population, participants did not identify themselves as having problems with their weight, diet, or physical function. This was despite their own reports to the contrary; of weight loss, eating difficulties, or a reduced ability

to complete activities of daily living. The view of such problems as 'expected', irremediable, or attributable to other comorbidities or ageing, meant that these problems were easily disregarded, or not seen as concerning. This is discussed further in section **9.4.3**.

Male patients have a higher prevalence of cancer cachexia, resulting in worse health outcomes compared to female cancer patients (492), with older adults known to be at higher risk of developing nutrition-related conditions, such as malnutrition, and age-related functional decline, as seen in sarcopenia, compared to younger adults with cancer (12, 13, 204). As discussed in section **3.2.1**, this thesis focused on older adults with cancer, therefore prevalence estimates of malnutrition, sarcopenia and cachexia, were expected to be higher than overall population estimates.

Additionally, recruitment from outpatients, as well as inpatients, was planned, but not achieved due to the pandemic. As shown in **Appendix 24**, 47% (14 of 30) of participants in group one were in their last year of life when screened for the conditions. As those with advanced or metastatic cancer are more likely to experience symptoms associated with malnutrition, sarcopenia, and cachexia (30), higher prevalence estimates in inpatients with metastatic disease (47% of group one), were also expected.

9.3.3 Overlap of malnutrition, sarcopenia, and cachexia

One-third of participants in group one (pre-COVID group) were diagnosed with all three conditions (**Table 38**), with statistically significant overlap seen between malnutrition and cachexia (**Table 31a** and **Table 31b**), although confidence intervals were wide due to the small study sample size.

These findings question the ability of current screening tools in distinguishing between malnutrition and cachexia in older adults with cancer, especially when a key diagnostic criterion for each condition is weight loss; with the MCASCO screening tool, a diagnosis of cachexia is only indicated if a weight loss > 5% is seen, regardless of any other symptoms, with the presence of other symptoms (e.g. anorexia, quality of life measures) only contributing to the severity of the cachexia (16). Malnutrition is defined by an inadequate intake or uptake of nutrients (133) - leading to an energy deficit, and therefore weight loss, and sarcopenia is defined by a loss of lean muscle loss, which may result in weight loss (17). Finally, cancer cachexia is also defined as ongoing loss of skeletal muscle mass (17), with the pathophysiology characterised by an ongoing negative protein and energy balance' (19), overlapping significantly with sarcopenia.

The results of my study suggest that sarcopenia is both a stand-alone condition, and one which frequently overlaps with both malnutrition and cachexia. There is a statistically significant

overlap between malnutrition and cachexia, with most patients presenting as malnourished also presenting as cachexic, suggesting a strong link between the two.

Although there was no statistically significant relationship between sarcopenia and malnutrition or sarcopenia and cachexia in this population, the clinical presentation of sarcopenia, and its overlap with frailty, which is characterised by increased vulnerability to poor resolution of homeostasis, after a stressor event (124), leading to functional impairment, is likely to be at play in this population. It is also noted that, due to the small study sample size, a significant relationship between sarcopenia and malnutrition or cachexia may be present, but not observed in this study. It has previously been suggested that there may be no single phenotype for cachexia, in that reduced nutritional intake (starvation-related malnutrition), and increasing age (sarcopenia), are fundamental characteristics of cachexia (18, 493), which further supports the interlink of the three conditions. A significant relationship was seen between Rockwood frailty score and sarcopenia diagnosis, with Rockwood score predicting a diagnosis of sarcopenia in univariate analysis, suggesting Rockwood score, or frailty assessment, may be a useful indicator of sarcopenia in this population.

A cross-sectional study looking at the overlap of malnutrition, sarcopenia, cachexia, and frailty in a hundred hospitalised older adults (aged ≥70 years) in Germany (494), of which 31% had oncological diagnoses, found that 63% of patients had at least one of the four conditions, with 8% experiencing all four conditions. This study also found a significant overlap between malnutrition and cachexia, with 93% of malnourished patients also identified as cachexic, but found that frailty and sarcopenia only occurred concurrently in 19% of patients, and sarcopenia and cachexia occurred simultaneously in 22% of patients (494). However, it is noted that the ESPEN consensus definition (140) was used to diagnose malnutrition, the Evans, 2008 criteria for cachexia (22), EWGSOP 2020 (59) definition for sarcopenia, and Fried et al., 2001 (495) criteria were used to diagnose sarcopenia, which, alongside the varying diagnoses included (31% oncology, 33% gastroenterology, 36% ‘other’) (494), make their results directly incomparable with mine.

Several theories have been presented regarding the overlap of malnutrition, sarcopenia, and cachexia. These include cachexia and sarcopenia categorised as ‘nutritional disorders’ under malnutrition (140), malnutrition and cachexia viewed as separate conditions (22), and sarcopenia used as a diagnostic criterion of cachexia (19). **Figure 18** presents a suggested overview of the relationships and overlap of malnutrition, sarcopenia, and cachexia, in older adults with cancer. More recent diagnostic criteria for malnutrition, in particular the GLIM criteria (145), have grouped the identification of these conditions together. Malnutrition has also previously been suggested as an umbrella condition (137), with multiple causes for the

condition of malnutrition itself, including 'sustained inflammation' caused by cachexia (183). Although these definitions and diagnostic criteria promote the interlinking of these three conditions, there is a risk of oversimplifying and amalgamating the three conditions, preventing the tailored management and treatment of the three conditions. As discussed in sections **1.2.2**, **1.3.4**, and **1.5.3**, the management strategies of these three conditions vary, which supports the requirement for disentangling the aetiology of these conditions, including the causes of weight loss and reduced physical function in older adults with cancer, to allow the appropriate management strategy to be implemented.

9.3.4 Understanding of malnutrition, sarcopenia, and cachexia

Despite the overlap of the conditions, my interviews highlighted a gap in knowledge regarding the overlap and relationships between nutrition and physical function. Physical function was viewed as a priority by participants, and its impact on quality of life, ability to complete daily activities, relationship with independent home living, and its implications upon commencing or completing anticancer treatment, were readily reported. Greater physical activity and mobility in people with cancer are known to improve functional health, energy levels, physical strength, and reported quality of life (496). As found in my interviews, patients are willing to start treatment (including increasing physical activity) to manage sarcopenia, once informed of its consequences.

However, the link between nutrition and physical function was only peripherally reported by participants, and only in relation to the health of others; reporting links between diet, energy, and ability to complete activities of daily living, but their connection between *their* diet and physical function was not made, except in retrospect when dietary intake improved and participants experienced an increase in energy and stamina.

9.3.4.1 The role of clinicians

Participants described how their reports of weight loss to clinicians were often not acted upon. The perception that HCPs did not acknowledge their weight loss, even when brought to their attention by patients, has previously been reported (497), with patients reporting frustration over the lack of management for weight loss, and a loss of confidence in HCPs knowledge. My findings expand upon this, with participants either self-advocating and pushing for support, or, conversely, resigning themselves to their reduced function, weight loss and poor health.

This echoes a qualitative study of general practitioners' (GP) views of malnutrition management, where malnutrition was seen as a secondary concern, compared to the patient's primary illness (498). Malnutrition was not prioritised against other nutrition-related concerns, such as obesity, with GPs citing a lack of resources as the main barrier – both of written

literature to provide to patients, and a lack of access to dietitians (498). GPs also viewed their role as 'firefighting', with malnutrition not considered part of the 'fire'; instead, clinicians focused on the cause of the weight loss, rather than the weight loss itself (498).

> *"When you think of general practice and when you think of fighting fires, for whatever reason I don't think nutrition is considered a fire" (498)*

Participants also reported not initially noticing their own weight loss, or when they did, views that poor nutrition, or worsening function, were not medical problems, prevented these concerns from being raised. Many barriers to recognition of malnutrition have been suggested, which include patients not recognising there is a problem, believing nutrition to be of low importance, and wishing to avoid 'unhealthy' high-calorie foods (424). These barriers were also exacerbated by clinicians, with barriers to raising concerns including a lack of awareness of nutritional screening, a similar belief that nutrition is not important, and a belief in patients' lack of interest in their own nutrition (424).

This feedback loop, (**Loop 2**) of clinicians believing patients are not interested, or belief that patients are not raising concerns about their nutrition or function, therefore these must not be concerning, negatively reinforces the belief that patients have regarding raising their own concerns, as they do not view nutrition or function as medical problems, or do not feel listened to by clinicians. This diagnostic overshadowing by clinicians confirmed participants' beliefs that their nutrition or function problems were minor, as they are not addressed (499, 500), affecting their perceptions of their required or possible treatments. This is seen in other problems such as breathlessness (499, 501), with breathlessness also seen as 'normal' and an expected part of the disease processes (499, 500), therefore ignored by both patients and clinicians. (499, 501).

This lack of engagement by clinicians has been suggested to be caused by a perceived lack of possible interventions for clinicians to initiate, with nurses having reported hesitance to discuss cachexia with patients affected due to a belief that little could be done to help (500, 502). This, in turn, deters patients from seeking advice based on prior unsuccessful experiences to elicit help, resulting in sadness, and resignation to poor nutrition (503). This could be considered a form of therapeutic nihilism, which is a major contributor towards reduced quality of life among older adults with cancer (504), with older adults with cancer not optimally diagnosed or treated (504, 505), due to a lack of evidence or knowledge about a condition, or belief in a treatment's ineffectiveness (506, 507). Clinician interviews were originally planned for the latter stages of this thesis but, due to the pandemic, were not

conducted. Further research into clinician perceptions of the three conditions, and methods to improve communication with patients regarding them, is required.

My thesis highlights the need for an improvement in the acknowledgement of, and subsequent treatment of, malnutrition, sarcopenia, and cachexia by clinicians. The benefit of identifying and distinguishing between the conditions lies in the ability to then treat or manage the condition in the most appropriate, patient-centred way. As previously highlighted, the treatment and management strategies for the three conditions vary due to their differing aetiologies, and relation to stage of cancer disease (12, 17, 27, 28). This is demonstrated most starkly when considering the alternate treatment plans for starvation-related malnutrition at the commencement of treatment, compared to the management of refractory cachexia in advanced disease (19, 23, 48). Management of eating-related distress often caused by anorexia and an inability to halt ongoing weight loss, and nutrition-impact symptoms (e.g., breathlessness [due to reduced muscle mass], nausea and vomiting, constipation (508)) from refractory cachexia, can be considered a main priority. In this instance, and in opposition to the treatment of starvation-related malnutrition, aggressive nutrition support would be inappropriate, and likely cause further distress (48). Therefore, to allow patient-centred care, it is imperative that these conditions be distinguished one from another.

The challenges with recognising the serious impact of these conditions are echoed in the office for national statistics mortality statics, which recorded listed causes and modes of death. Only 75 cases were listed with malnutrition as an ICD-10 cause of death in 2020 in England and Wales (E40-46 Malnutrition), averaging 80 cases a year over the last five years (509). Similarly, cachexia was listed as the cause of death in only six cases in 2020 (R64 Cachexia), averaging 14 cases a year over the past five years (509). Further, it is only recently, in 2017, that sarcopenia has been provided with its own ICD-10 code, M62.84 (510). This is despite cachexia affecting between 11 and 90% of patients, depending on cancer stage and diagnosis (27), with 10 – 30% of cancer deaths thought to be attributable to cancer cachexia (511-513).

9.4 The role of screening for malnutrition, sarcopenia, and cachexia

9.4.1 Combining and streamlining screening tools

Part of the original aim of this thesis was to determine if the three individual screening tools for malnutrition, sarcopenia, and cachexia could be combined into one, clinically useful screening tool, able to identify and differentiate the three conditions in older adults with cancer. My results suggest that key predictor variables (**Table 40**) could be used as a starting point for future research into streamlining the screening tools in older adults with cancer. This would include percentage meal consumption (as a measure of dietary intake), and sunken

temples (as a measure of visible emaciation) for malnutrition, Rockwood clinical frailty score for sarcopenia, and use of percentage monthly weight loss (to assess for rapid weight loss) in cachexia; all of which were found to be acceptable to screen for by the participants in my study.

My results also showed that completion of physical function measures were poor (see **Table 27**) However, a correlation between several physical function measures, including skeletal muscle index (measured using BIA), and simpler assessments of physical function and muscle, such as timed up and go, and mid-arm circumference, are shown in **Table 39**, suggesting simpler measures of physical function or performance may be as useful as a proxy for muscle mass loss, and may be more acceptable to patients.

Both the clinical frailty score (Rockwood) and comorbidity index (Charlson) were feasible for use in this population (100% completion), as measures were completed by the researcher, and can be completed by any clinician, rapidly, with reference to clinical records and patient observation. Although there is no international standard for the measurement of frailty (514), the Rockwood clinical frailty score demonstrates high validity and reliability as an adverse outcome predictor for hospitalised older adults (515, 516), suggesting its use in this population is appropriate.

As seen in section **7.1.4**, 93% of those diagnosed with moderate or severe malnutrition, and 100% of those diagnosed with cachexia reported a 5% or greater weight loss. Weight loss is a core marker for both malnutrition and cachexia (19, 150), however, the results of this study suggest due to the overlapping clinical presentation, diagnostic criteria, and patient perceptions, weight loss *alone* cannot be used to distinguish between malnutrition and cachexia, yet is important for assessing development and severity of the conditions (16, 19, 135).

Findings from the qualitative interviews confirm the importance of visual markers of malnutrition and weight loss that can be observed by participants. Participants reported that problems with their nutrition or function, were often prompted by either family, or themselves noticing visible changes in either their weight (rapid weight loss), their function (use of mobility aid), or their diet (reduced portion sizes). Reliance on visible changes as a sign of advancing illness has been reported previously (500), with visible weight loss, in particular, causing self-consciousness and distress, as it was an external sign of an internal cancer (497). Additionally, visible reduction in portion sizes, and the associated lack of appetite have previously been reported as a source of distress for patients with cachexia (497), echoing my

findings. However, importantly, slow or small weight losses were not seen as concerning, and were easily disregarded or attributed to other comorbidities or ageing.

Results of my study suggest the use of frailty assessment in the diagnosis of sarcopenia. There are close links between the aetiology and clinical presentations of sarcopenia and frailty, with sarcopenia often viewed as a major component of frailty (125). Due to my limited assessment of frailty, it is not possible to draw further conclusions about the use of simple frailty assessments to predict sarcopenia in older adults with cancer, but this would warrant further investigations due to the significant overlap in the physical presentations of frailty and sarcopenia (517) and current management strategies and treatments (518).

Identifying sarcopenia, or other aspects of frailty in older adults is complicated by perceptions that the ageing process is responsible for deteriorations in function or appetite; my participants expressed beliefs that nutritional problems and functional decline were a normal part of ageing. Misattribution of symptoms (weight loss, reduced appetite, or poor function) to causes such as ageing, or an assumption that they were a normal part of the cancer disease process resulted in these problems being overlooked, or disregarded by both participants and their clinicians. This was despite participants reporting physical function to be a priority, with many keen to make changes and increase their physical activity. This dissonance in views may present barriers to screening advice uptake, although, as found in this study, patients have reported willingness to start treatment (including increasing physical activity) to manage sarcopenia once informed of its consequences (519).

A rapid decline in weight, nutritional intake, or physical function was reported as concerning by participants, but a lack of engagement by clinicians, meant that participants felt HCPs did not respond as they would wish them to regarding their concerns. This resulted in participants being placed 'between a rock and a hard place', of having concerns about their nutrition or physical function that were impacting on their health and quality of life, but not having anywhere to turn. Participants reported frustration, anger and despair, perceiving their weight loss as being trivialised, with participants either fighting and self-advocating for support, or, resigning themselves to poor health.

9.4.2 Patients' views and experiences of screening for malnutrition, sarcopenia, and cachexia

Screening for malnutrition was seen as acceptable. In addition, I found that the screening questions for sarcopenia and cachexia were acceptable. Missing data were minimal, other than functional markers as previously discussed. Overall, results indicate the completion of the

screening tools was feasible, up until diagnosing 'probable' sarcopenia using the EWGSOP 2019 criteria (17). See **Figure 1** for stages of the algorithm.

There was a poor recall of screening questions asked; however, participants were more likely to remember the physical measures, such as sit-to-stand or hand-grip strength. Completion of the anthropometric measures varied, with participants declining, or being unable or unwilling to complete some of the physical measures (e.g., chair stand test, timed up and go). Routine anthropometric measures, e.g. height, weight, were most readily obtained (91.7% – 97.2%), compared to the additional functional measures, e.g. chair stand test, timed up and go, or measures of skeletal muscle mass, i.e., bioelectrical impedance analysis (30.8% – 41.7%), see **Table 27**.

Issues included participants' perceptions of their ability to complete the measure, in addition to those who were physically unable to do so. Analysis of those who declined, compared to those who were unable to complete these measures was planned, but was not possible due to the small sample size.

Many benefits to completing the screening measures were reported by my participants, which included; screening providing an opportunity to raise and share concerns, an opportunity to consider their nutrition and function – which they may not have considered before, and screening being viewed as an intervention in itself, by reassuring participants they are able to complete physical measures which translate into increased confidence in activities of daily living. However, barriers were also reported, with some participants reporting they perceived little benefit from the screening process, as they believed they were functionally and nutritionally well, or at low risk of developing these conditions. Participants' perceptions of their risk of developing problems with their nutrition or function were influenced by multiple factors, but often resulted in a reduced perception of their personal risk of developing these problems. Factors considered protective against these problems included past health behaviours, including following a 'healthy' diet, or staying active. This highlights the need for patient education regarding nutrition and physical function; to combat generic health messages and patient assumptions, to enable management of these conditions.

Optimism bias, the overestimation of the likelihood of positive future events, and the underestimation of the likelihood of further negative events, is a common phenomenon (520, 521), and was demonstrated by several participants regarding their risk of developing nutritional or functional problems. This is likely compounded by a lack of understanding of the causes and consequences of these conditions, further reducing participants' risk perceptions (522), with some authors concerned that unrealistic optimism results in lower motivation and

engagement in health-protective behaviours (523, 524), or in this case, engagement with screening.

Loop 3 Figure 17: Feedback Loop Diagram, describes the potential impact of routine screening for malnutrition, sarcopenia, and cachexia in older adults with cancer. Participants reported several benefits to the screening process for the three conditions, which included screening being seen as; an opportunity to consider and discuss any nutritional or physical function concerns, an opportunity to share concerns and worries, and providing reassurance of the ability to complete simple physical actives e.g., sit-to-stand, with the presence of a health care worker providing assurance. Engaging in physical activity allows patients to regain confidence in their function and physical abilities (496). Findings from my interviews suggest that screening, which includes physical measures of strength, provides a similar benefit for those who are concerned about their ability to complete basic ADLs whilst in hospital.

These benefits of screening could help mitigate the barriers to participants receiving support and interventions for their nutrition or physical function; of poor knowledge, overshadowing, and poor risk perception. Screening also provides an opportunity to educate and increase understanding of conditions (519), which then impacts upon a patients' perceptions of the risks of developing said conditions (525, 526), and can promote preventative behaviours (525).

This signposting, and provision of information or treatment could then positively impact upon the risk of diagnostic overshadowing, and may prevent these conditions from being overlooked by clinicians. This, in turn, would prevent patients from being placed in between a 'rock and a hard place', as screening provides an outlet for concerns, and an opportunity to seek support. It is noted, however, that to manage this, overcoming barriers, such as patients' staunch positive perceptions of their current health, and assumptions regarding past protective behaviours, as well as the enormity of diagnostic overshadowing and the physical and mental impact of a cancer diagnosis on a patient, must be considered. As shown, the timing of advice, and consideration of barriers, such as patients being too unwell to be receptive to advice, are important in implementing effective screening practices (185, 405).

9.4.3 The problems with perceptions

Perceptions of general nutrition, and nutritional and functional problems were reported by participants in the interviews. These included perceptions regarding 'healthy' diets and eating, perceptions regarding weight loss during treatment, and perceptions around ageing, weight, and function, which influenced participants' opinions and reactions to their own weight loss or functional problems.

These findings highlight a lack of disease-related knowledge regarding nutrition and physical function, whereby generic public health messages, aimed at combatting obesity and other non-communicable diseases, eclipsed advice for managing nutrition and functional problems in old age, or during a cancer diagnosis. These messages were often reinforced by either the absence of advice from health care professionals during cancer treatment, or advice to stay 'active', or follow a 'healthy' diet, confirming beliefs in the need to continue to follow their current nutrition or physical activity tendencies. These findings are supported by the recent literature, with obesity viewed as the dominant nutritional issue in primary care, and malnutrition viewed as a secondary concern when compared to other comorbidities (498).

Patients also perceived nutrition and physical function problems as a normal part of both the ageing process, and of the cancer journey. Beliefs about the inevitable decline in nutrition and function among older adults have previously been reported, with beliefs that less food was needed when older, with an expected decline in dietary intake with age attributed to reduced mobility after retirement (503). This was despite various lived experiences and acknowledgement of the general need to stay active, fit, and consume adequate nutrition (503), as also seen in my study.

The overarching impact of a lack of knowledge or awareness of malnutrition, sarcopenia, and cachexia, and about nutrition or physical function in relation to cancer, is a fundamental cause of the difficulties participants reported experiencing. **Loop 1**, **Figure 17: Feedback loop diagram** illustrates the impact of this core misunderstanding, with this lack of knowledge leading to a reduced risk perception, which in turn contributes to participants experiencing dissonance in their views regarding nutrition and physical function; of both not being at risk (despite lived experiences of malnutrition or functional impairment), and accepting the inevitability of poor appetite, weight loss, and reduced mobility, caused by the cancer, and other factors such as ageing.

A lack of awareness of these conditions and terms has been seen before, with one study finding that only 9% of a cohort of community-dwelling older adults (mean age 68 years) knew what sarcopenia was (519). The term 'malnutrition' was more commonly known in this group, which is in concordance with previous findings, with 97% of a group of community-dwelling older adults reporting in a survey to have heard of 'malnutrition' (527). However, this study did not assess participants' understanding of malnutrition. These interviews suggest that although this term is more widely heard of, it remains a misunderstood term.

A recent qualitative study (528) investigating health care professionals (HCPs) and patients' opinions of the term 'malnutrition', found that the term 'malnutrition' was associated with

negative connotations, and should be avoided. My interview findings suggested that malnutrition was a 'clinical' term, which was not understood by patients, and was even seen as "*not a nice word*", suggesting its use is not helpful when discussing nutritional problems. Additionally, participants reported that 'malnutrition', 'sarcopenia' and 'cachexia', were too technical, unfamiliar, and were akin to complex medicine names, and therefore not understood.

A misunderstanding of malnutrition in particular, led to a belief that nutritional concerns were considered minor, as "*it's not going to happen to me*", and, if issues arise, "*we'd just do something about it*". This included views that malnutrition, or functional problems were minor problems, or were seen as conditions faced by low-income countries, which resulted in participants believing these conditions would not affect themselves, or if they did, they would be easily fixed. These beliefs were held despite several participants experiencing, and reporting malnutrition, or functional problems.

Discrepancy in self-reported nutritional status, and self-reported strength, against objective measures, has previously been reported (519, 527, 529), regardless of acknowledgement of the importance of muscle health, patients were often unaware of their own muscle health (519). Poor perception of own body weight, and self-perceived nutritional status is also seen in older adults (aged ≥65yrs), with one study finding half of 'healthy weight' (BMI: 23 – 30kg/m^2) participants perceiving themselves as overweight (527). Low self-perception of malnutrition was also seen in hospitalised older adults (aged ≥60yrs, mean 82 years), with no agreement seen between objective and self-perceived nutritional status seen, where 67.7% of malnourished patients did not realise they were malnourished (529). However, these findings expand upon this, suggesting that a lack of knowledge regarding these conditions is a possible reason for this disconnect.

There is little current literature regarding risk perceptions and malnutrition, however, this is well documented in other conditions, such as smoking and risk of ill health, with low perceived vulnerability and optimism bias contributing to continued cigarette use (526). Additionally, perceptions of risk are often driven by past experiences, with greater knowledge about a disease associated with preventative behaviours (525). This suggests that methods such as screening, which may present an opportunity to address misconceptions about these conditions, could contribute to the solution to this problem (**Loop 3**). However, optimism bias, the overestimation of the likelihood of positive future events, and the underestimation of the likelihood of further negative events, was also expressed by participants regarding their risk of developing nutritional or functional problems. This is likely compounded by a lack of understanding of the causes and consequences of these conditions, further reducing

participants' risk perceptions (522), with some authors concerned that unrealistic optimism results in lower motivation and engagement in health-protective behaviours (523, 524), or in this case, potential engagement with screening.

As demonstrated in **Loop 2**, **Figure 17: Feedback loop diagram**, diagnostic overshadowing negatively impacts many aspects of patient care. 'Diagnostic overshadowing' is the process of overlooking or disregarding symptoms by assuming they are explained by another condition or diagnosis, and is a term most commonly used in mental health fields (530). However, it has also been suggested to be seen with symptoms such as breathlessness (499) and fatigue (531), which can also be misattributed to other conditions, or ageing (503), and are seen as an accepted and normal inevitability (532), and therefore ignored (507). Diagnostic overshadowing leads to inadequate or delayed treatment of the presenting symptom (533), which was reported by my participants who experienced weight loss. This overshadowing was amplified by my participants' concerns about their nutrition or physical function being overlooked and underplayed by clinicians, with nutrition in particular not prioritised.

Participants reported that weight loss and functional concerns were attributed to their cancer by clinicians, and therefore were dismissed. However, participants themselves also engaged in diagnostic overshadowing, blaming problems such as weight loss, poor appetite, or reduced function on other causes, including their own comorbidities (e.g., chronic obstructive pulmonary disease), upon their advancing age, or upon the cancer itself. This misattribution has also been reported in the field of mental health, with patients not knowing if the cause of a symptom is physical, or related to their mental health (534). As with breathlessness (501), weight loss is often misattributed to ageing, with older adults not viewing weight loss, reduced appetite, or reduced dietary intake as a problem (535), with concerns about eating and weight loss decreasing with age (536).

This was expanded upon by this participant population, with their cancer diagnosis overwhelming many aspects of their lives, with the cancer and its treatments overshadowing other major symptoms, such as one participant with a gastrointestinal obstruction being more concerned over the ability to take their medications orally, than to eat.

9.5 Conclusions

This mixed-methods study confirms the feasibility of recruitment of older adults with cancer from inpatient settings, however difficulties recruiting during the pandemic are noted, and although recruitment ratios remained high (3:1), a reduction in the number of patients appropriate to approach due to the pandemic may impact upon future studies and recruitment numbers. Difficulties recruiting from outpatient settings suggest a requirement to imbed the researchers within outpatient multidisciplinary teams or clinics, to increase researcher visibility and study awareness.

Data indicated a high prevalence of malnutrition, sarcopenia and cachexia in this population, showing a requirement for addressing these issues in older adults with cancer. The feasibility of screening in this population is demonstrated, but attention needs to be paid to the ability of this population to complete additional mobility-based physical measures, although their inability to complete measures may be considered an assessment in itself.

This study highlights the major overlap of these three conditions, in particular malnutrition and cachexia, but showed a large subset of participants with evidence of all three conditions, highlighting the need for a method to distinguish between each condition. Results suggest candidate predictor variables for malnutrition, sarcopenia and cachexia, with further investigations required to assess their suitability to distinguish between these three conditions in older adults with cancer.

In addition to the clinical burden of these conditions, results of the interviews show the burden nutrition and physical function problems placed on patients, and suggest a need for routine screening for these overlooked conditions. At present, barriers to addressing malnutrition, sarcopenia and cachexia include both patient knowledge of these conditions and the roles they play in their cancer journey, and barriers presented by clinicians, such as diagnostic overshadowing, resulting in these conditions being overlooked and underplayed, and a lack of knowledge about the conditions or their effective interventions. Appropriate, well-conducted screening may provide a method to address these barriers, and provide patients with a positive experience and management of malnutrition, sarcopenia, and cachexia.

9.6 Summary

In this chapter, I have discussed the findings of my mixed-methods study synthesis. Primary findings are; malnutrition, sarcopenia, and cachexia are highly prevalent, and overlapping conditions, in this population of older adults with cancer. Visual makers of decline (physical appearance and reduced portion sizes) were seen as possible predictor variables of malnutrition in univariate logistic regression, and confirmed as important markers for participants in qualitative interviews. Rockwood clinical frailty score for sarcopenia, and rapid weight loss for cachexia, were also identified as possible predictor variables. However, the efficacy of screening tools that detect established conditions, is questioned.

Further, despite the high prevalence of these conditions, they are often overlooked, both by patients who have a lack of understanding about these problems, their impact and relation to their personal health, and they are perceived as disregarded by clinicians, with these conditions overshadowed by the cancer diagnosis. Conflictingly, these conditions and their symptoms are also seen as inevitable aspects of ageing and the disease process, despite assertions that "*it's not going to happen to me".* This dissonance requires further exploration, but presents a unique barrier to addressing nutritional and physical function problems in older adults with cancer.

A synthesis of these results with the findings of the systematic review of malnutrition markers presented in **Chapter Four**, and the systematic review of patients' experiences in **Chapter Five**, alongside a discussion of the thesis' main aim and research questions, will be presented in **Chapter Ten**.

Chapter 10: Discussion

This chapter will integrate the findings of the two systematic reviews **Chapter Four** and **Chapter Five**, with the results of the mixed-methods study synthesis **Chapter Nine**, to address the thesis' overarching research aim. The strengths and limitations of this thesis, alongside the clinical and research implications of this work, will also be discussed.

10.1 Thesis aims

The overarching aim of this thesis was:

- To understand better the prevalence, detection, assessment, and patients' experiences of malnutrition, sarcopenia, and cachexia in older adults with cancer.

The research questions were:

1. What is the relationship between markers of malnutrition and clinical outcomes in older adults with cancer, in the published literature?
2. What are patients, their families, and carers' experiences and views of nutritional screening, as identified in the published literature?
3. What is the prevalence and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer?
4. What are the experiences and views of older adults with cancer regarding screening for malnutrition, sarcopenia, and cachexia?

With the research objectives:

1. To identify, synthesise, and critically appraise the published evidence regarding commonly used markers of nutritional status and clinical outcomes in older adults with cancer.
2. To identify, synthesise, and critically appraise the published evidence regarding patients, their families and carers' views and experiences of nutritional risk screening.
3. To gain exploratory estimates of the prevalence of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer.
4. To investigate the feasibility of conducting a subsequent adequately powered study to develop, refine, and test a single, clinically relevant screening tool, able to identify and distinguish between elements of malnutrition, sarcopenia, and cachexia in older adults with cancer.

5. To explore the interrelationships and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer.
6. To explore and understand patients' experiences and views of the clinical assessment and management of malnutrition, sarcopenia, and cachexia.

The mixed-methods study findings were discussed in **Chapter Nine**. To integrate all my findings with regard to the thesis' research questions, I have used a similar approach to my mixed-methods synthesis, using an integrative grid showing summary findings from my systematic reviews and mixed-methods synthesis. See section **3.6** for methodological approach. The findings from the different methodological approaches in the whole thesis are synthesised in **Table 43**, and will be discussed in this chapter. Finally, a summary discussion, addressing the overall thesis research question and a summary of novel findings, is presented in section **10.5**. The thesis' strengths, limitations, and the clinical and research implications of this work are presented thereafter.

Table 43: Modified critical interpretive synthesis of systematic review findings and mixed-methods study results

Research questions	Systematic review of markers of malnutrition	Systematic review of patient experiences of nutritional screening	Mixed-methods study results	Synthesis of findings
RQ1: What is the relationship between markers of malnutrition and clinical outcomes in older adults with cancer in the published literature?	▪ Fifteen heterogenous markers of malnutrition identified ▪ Variable and arbitrary thresholds for most markers ▪ Reduced food intake associated with mortality ▪ Very low body mass index (≤18kg/m^2) associated with poorer clinical outcomes ▪ Prognostic nutritional index associated with poorer clinical outcomes, but measures inflammation, and does not assess dietary intake, questioning utility as a marker of malnutrition	▪ No findings related to this research question	▪ Overlap of markers of malnutrition and cachexia highlighted, questioning the ability to distinguish conditions in high-risk groups, such as older adults with cancer, using currently employed markers of malnutrition and cachexia ▪ Due impact of the pandemic on longitudinal outcomes, unable to investigate the relationship between markers of nutritional status and clinical outcomes ▪ Meal consumption and visual appearance associated with malnutrition diagnosis, Rockwood frailty score with sarcopenia, and rapid weight loss with cachexia	Many heterogeneous markers with variable and arbitrary thresholds exist for all three conditions. Reduced food intake and very low body mass index appear to be important markers of malnutrition. Importance of distinguishing between inflammatory and starvation related causes of nutritional problems noted.
RQ2: What are patients, their families, and carers' experiences and views of nutritional screening in the published literature?	▪ No findings related to this research question	▪ Nine papers, including five qualitative interview papers were identified ▪ No papers were identified that captured family or carer experiences ▪ Nutritional screening was seen as 'acceptable' by most, but some were unclear on what was being assessed, or the aim of nutritional screening ▪ A misunderstanding of malnutrition was seen, with a focus on following a 'healthy diet' prioritised, and a lack of knowledge	▪ Screening process is seen as 'acceptable' ▪ Screening is viewed as a positive intervention by some; an opportunity to raise concerns, or consider nutrition or functional issues which had not been thought through before, reassurance of ability to complete simple measures of function, and beneficial to mental health as able to share concerns ▪ No benefit perceived by some as did not see self as at-risk of	Processes of screening for conditions seen as acceptable; questionnaire-based aspects well completed (>99%). Although physical measures are seen as beneficial, poor uptake during the screening process. A misunderstanding of malnutrition, particularly its causes and consequences, results in reduced risk perception by patients, and

		regarding the causes and consequences of malnutrition was also reported ▪ These combined often resulted in a rejection or disbelief of nutritional screening results and associated recommendations	nutritional or functional problems, often despite lived-experience of these issues	associated reduced perceived threat of these conditions. Screening may act as an intervention to raise awareness of nutritional and functional issues, and act as a health intervention in itself, with physical measures of function promoting increased mobility and confidence in some.
RQ3: What is the prevalence and overlap of malnutrition, sarcopenia, and cachexia in a group of older adults with cancer?	▪ Overlap of diagnostic criteria and definitions for malnutrition, sarcopenia, and cachexia identified: - Loss of muscle mass, loss of muscle strength/function and weight loss are key diagnostic criteria for all three conditions - Body mass index, disease state, catabolism/inflammatory response and oral intake are also commonly used criteria	▪ No findings related to this research question	▪ 83% with evidence of one or more of the conditions ▪ 30% with evidence of all three conditions ▪ Substantial overlap between conditions clinically, but not recognised by participants - 94% with cachexia also identified as malnourished - 61.5% with severe malnutrition identified as sarcopenic - 52.9% with cachexia identified as sarcopenic	The overlap of diagnostic criteria and definitions for malnutrition, sarcopenia and cachexia may translate directly into the overlap of diagnoses of the conditions at a population level. Findings suggest an inability to distinguish between malnutrition and cachexia using current screening tools and condition markers in older adults with cancer.
RQ4: What are the experiences and views of older adults with cancer regarding screening for malnutrition, sarcopenia, and cachexia	▪ No findings related to this research question	▪ No findings related to this research question	▪ Discordance in uptake and acceptability of physical measures between quantitative and qualitative findings; measures viewed as motivational during interviews, but poor uptake during screening process;	Discordance in uptake and acceptability of physical measures between quantitative and qualitative findings; measures viewed as motivational during interviews,

			▪ High declination of measures due to assumed inability to complete; if completed act as an intervention to aid physical activity ▪ Screening presents an opportunity to highlight and address nutritional and physical function problems ▪ Many barriers presented to clinical management of conditions; conditions overshadowed by the cancer diagnosis, ignored by clinicians, compounded by low risk perception by patients of developing these conditions ▪ Timing of intervention critical in the uptake of advice ▪ Function prioritised over nutrition	but poor uptake during the screening process. High decline of measures due to assumed inability to complete; if completed act as an intervention to aid physical activity. Screening presents an opportunity to highlight and address nutritional and physical function problems. Many barriers presented to clinical management of conditions; conditions overshadowed by the cancer diagnosis, ignored by clinicians, compounded by low risk perception by patients of developing these conditions. Timing of intervention is critical in the uptake of advice. Physical function is prioritised over nutrition by patients; lack of understanding of the relationship between the two

Thesis aim: To understand better the prevalence, detection, assessment, and patients' experiences of malnutrition, sarcopenia, and cachexia in older adults with cancer.

▪ Malnutrition, sarcopenia, and cachexia are highly prevalent, overlapping conditions, that are overlooked and under-recognised in older adults with cancer

- Overlapping definitions and diagnostic criteria contribute to difficulty in distinguishing between conditions; in particular overlap of weight loss, loss of muscle mass, and strength
- Significant overlap between malnutrition and cachexia questions the discrete nature of these conditions in older adults with cancer
- Misunderstanding of conditions, their aetiologies, risk factors, and beliefs that being overweight or following a 'healthy' diet precluded development of problems resulted in conditions being overlooked
- Consideration must be made for the aetiology of key diagnostic criteria e.g., weight loss, to aid in the management of these conditions

▪ Streamlined predictor variables appear useful in clinical practice for differentiating malnutrition (dietary intake and visual appearance [sunken temples, low body weight, very low body mass index]); cachexia (rapid weight loss and inflammation); and sarcopenia (frailty [Rockwood]) from one another, with visual markers both clinically relevant and important markers for patients and relatives in detecting problems. However, further investigations in a larger sample are needed to confirm findings

▪ It is feasible and acceptable to screen for malnutrition, sarcopenia, and cachexia in older adults with cancer using current screening tools, however, poor completion of physical function measures by hospitalised older adults with cancer, combined with difficulties distinguishing between the conditions, and barriers to identification and management, which include patients' perceptions and overshadowing of the conditions by patients and clinicians alike, mean further work is required to enable simplification of screening, differentiation between, and treatment for, the three conditions

- Screening for malnutrition, sarcopenia, and cachexia, may present opportunities to address barriers and prevent overshadowing by disease or ageing, but consideration of the barriers, including the timing of interventions, poor completion of some physical function measures, and patients perceived low risk of developing nutritional or physical function problems
- Patient and clinician perceptions of these conditions must be challenged to improve patient care and symptom management, particularly regarding the assumed inevitability of these conditions, and the discordant view they play in patient's personal health
- Current screening criteria indicate an active problem, rather than warning signs of conditions. Assessment of pre-condition markers needed, with an associated shift in clinical practice and understanding of the conditions in high-risk older adults with cancer.

10.2 Prevalence and overlap of malnutrition, sarcopenia, and cachexia

In my study, the vast majority of participants had evidence of either malnutrition, sarcopenia, cachexia, or a combination of these, with a third of participants showing evidence of all three conditions. As shown in **Table 18**, there is substantial overlap between the definitions and diagnostic criteria for each of the three conditions. In particular, there is extensive overlap of the use of weight loss and loss of muscle mass between criteria for malnutrition and cachexia, and loss of muscle function in all three conditions. This may have contributed to the significant overlap seen between malnutrition and cachexia, and substantial overlap of all three conditions (**Figure 16**).

My interpretation of the relationship between the three conditions is shown in **Table 18**, with malnutrition encompassing three domains, of; i) overnutrition e.g., obesity (135), ii) micronutrient abnormalities, e.g., vitamin deficiency such as thiamine deficiency in alcoholic liver disease (537), and iii) protein-energy malnutrition, caused by reduced dietary intake (i.e., starvation), or increased nutrient demand (e.g., wound healing) (137), with protein-energy malnutrition also resulting from inflammation-related malnutrition, produced by a disease process, e.g., catabolism, in this incidence, cachexia, with inflammation-related increased catabolism leading to inadequate protein-calorie intake in the context of increased demand) (153). That is, inflammation, by reducing appetite (489), causes malnutrition through both increased nutritional needs and reduced nutritional intake (153, 538), with both protein-energy malnutrition and catabolism contributing to the development of secondary sarcopenia (466).

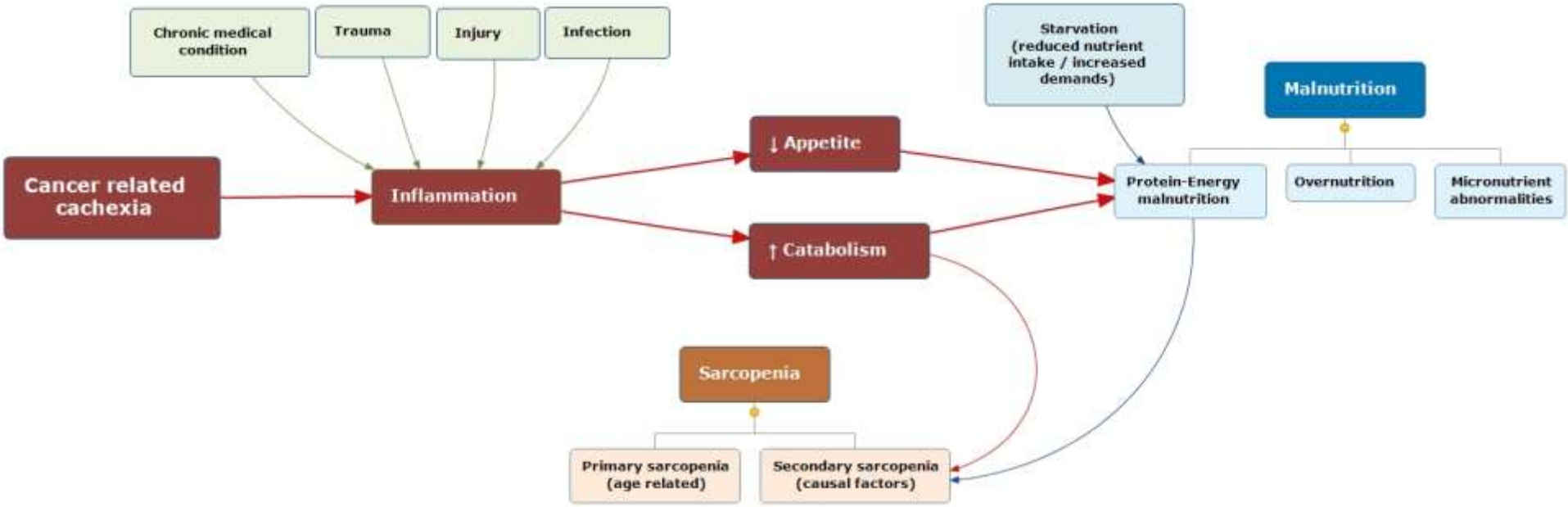


Figure 18: Suggested relationships and overlap between malnutrition, sarcopenia, and cachexia in older adults with cancer

Diagram detailing the proposed relationship between malnutrition, sarcopenia, and cachexia in older adults with cancer. Malnutrition encompasses the domains of; i) overnutrition, ii) micronutrient abnormalities, and iii) protein-energy malnutrition. Cancer-related cachexia causes inflammation, resulting in reduced appetite and increased catabolism; increasing nutritional needs and reducing nutritional intake, resulting in protein-energy malnutrition. Other non-cancer causes of inflammation, including trauma, injury or infection are noted, alongside alternate causes of protein-energy malnutrition through starvation.

10.2.1 Malnutrition and cachexia

The results of my study support the current literature (18, 23, 133) that suggests cachexia is not a stand-alone condition from malnutrition, with the inflammatory processes of cachexia, its impact on appetite, and the consequential anorexia, resulting in either protein-energy malnutrition (starvation), inflammation-related malnutrition, or both (21, 28, 35); with those identified as cachexic with significant weight loss invariably malnourished, and those with evidence of cachexia without significant weight loss at high risk of developing malnutrition.

Pre-cachexia, however, may be present in the absence of malnutrition, but would not be identified using current cachexia screening tools, e.g., MCASCO (16) due to the reliance on significant weight loss to identify cachexia (16, 22). Additionally, significant weight loss alone can trigger a diagnosis of cachexia using the MCASCO (16), with factors such as inflammation or anorexia used to indicate the severity of the condition; with 'mild' cachexia indicated with a weight loss >10% without any other indicators, or 'moderate' cachexia on weight loss alone if weight loss >15% in the past 12 months (16). Therefore, rapid weight loss caused by starvation e.g., gastrointestinal obstruction, could be falsely identified as cachexia using the MCASCO.

Malnutrition, in the form of protein-energy malnutrition, can however exist in the absence of cachexia in older adults with cancer, e.g., starvation-related malnutrition caused by gastrointestinal obstructions, or treatment-related adverse effects such as radiation-induced mucositis (12, 153, 154). As demonstrated in **Table 40**, malnutrition-specific factors, such as percentage meal consumption, which equate to 'calories-in', could be used to help identify patients who are experiencing protein-energy malnutrition (starvation) from a lack of nutrient intake.

However, for many older adults, it is difficult to distinguish protein-energy malnutrition from cachexia using single point-in-time data, or using current screening tools due to the overlap of diagnostic markers. Inflammation is a key characteristic of cachexia, and, inflammation in older adults with cancer *may* be cancer-related cachexia, but could also be due to cancer treatment (539), or from co-morbidity-related inflammation e.g., chronic obstructive pulmonary disease (540), cardiovascular disease or inflammatory bowel disease, or acute inflammation such as injury or infection (538, 540).

It is this factor that contributes to the difficulties in distinguishing between protein-energy malnutrition-related weight loss, and inflammation-related (catabolic) weight loss in older adults with cancer, and shows a need to assess the aetiology of inflammation and weight loss.

Longitudinal follow up of inflammatory markers, appetite, meal consumption (to provide an estimate of nutritional intake), response to increased nutrient intake, and monitoring of disease status in older adults with cancer could identify those in whom protein-energy malnutrition is a significant contributing factor of weight loss, and those for whom reversal of protein-energy malnutrition alone is insufficient, suggesting cachexia.

As intimated, **Figure 18** proposes that cachexia leads to, or, in the case of someone who is already experiencing protein-energy malnutrition, accelerates, malnutrition; with the inflammatory process causing an increased nutrient demand, and/or reduction in nutrient uptake or utilisation (150), causing malnutrition. However, this is not a cyclical relationship. Although malnutrition in itself does not cause cachexia, the presence of malnutrition may worsen cachexia. Malnourished patients are less likely to tolerate anticancer treatments, increasing the risk of cancer progression (13), with a consequent increased severity of cachexia. Malnutrition may therefore worsen cachexia, which then leads to a vicious cycle between the two.

Anorexia, without weight loss, could be an early warning sign for cachexia in older adults with cancer (19). It is at this point that inflammatory markers should be checked to determine if a patient is pre-cachexic (19), as there are more options for interventions for cachexia (outside scope of this thesis), *before* cachexia causes malnutrition, and the associated negative clinical implications (19, 23, 513). Early multimodal interventions are more likely to be effective in pre-cachexia, and therefore have the potential to prevent malnutrition and other consequences of cachexia (19, 23).

This would require a change in both practice and attitudes currently held regarding nutritional and physical function problems in older adults with cancer, of implementing nutritional and physical function therapies *before* the onset of major negative clinical outcomes e.g., significant weight loss, physical decline, and the associated hospitalisation when patients are unable to cope at home or unable to complete anticancer therapies (10, 36, 93, 159).

10.2.2 Sarcopenia, malnutrition and cachexia

Both malnutrition and cachexia can contribute to secondary sarcopenia; through either poor nutrition (in particular inadequate protein), or disease-related loss of skeletal muscle mass (inflammation) (17). In addition, sarcopenia may also present with muscle loss, and therefore overall weight loss (17) and has overlapping diagnostic criteria with cachexia (of assessment of lean body mass) also causing difficulties in distinguishing between sarcopenia and the other conditions. (17, 40).

My findings are consistent with the view that secondary sarcopenia is related to malnutrition and cachexia (17), with both catabolism and protein-energy malnutrition contributing to the development of secondary sarcopenia (**Figure 18**). Despite the overlap of a third of my study participants showing evidence of all three conditions, sarcopenia is in itself highly prevalent in this population, and is also shown as present in isolation, in the absence of malnutrition and cachexia. This supports the need to screen for each of the three conditions, as, although sarcopenia can exist in isolation, results of my thesis show the interrelationships of the three conditions, and the need to identify and manage the conditions collectively, in older adults with cancer.

10.2.3 Summary

It is important to determine the aetiology of weight loss, as, an assumption that weight loss is caused by protein-energy malnutrition alone, and subsequent treatment with increased nutrient provision, would not be an appropriate sole management strategy for inflammation-related weight loss. Results of my study show that these conditions often do not exist in isolation, and although provision of adequate nutrition may stem some of the weight loss if inadequate nutritional intake is present, nutrient provision alone will not resolve weight loss caused by inflammation (28, 153). Instead, a multidisciplinary approach, with identification and appropriate management of each condition, is required – with repeated assessments over time to allow early identification of concerns. Assessments of the causes of inflammation and weight loss, are required, including whether inflammation-related weight loss can be ameliorated with nutritional interventions, or if symptoms relief – including support for family and carers – should be the focus of care, such as with refractory cachexia (19, 538).

10.3 Identifying the truly 'at risk'

Treatments for malnutrition, sarcopenia, and cachexia in older adults with cancer are complex (52, 102, 171, 172), with many components difficult to manage, or irreversible, in advanced stages (17, 19). Yet current practice is to wait *until* nutrition and/or physical function have deteriorated before offering interventions. Screening tools for each of these conditions only identify risk *once* significant weight has already been lost, or significant functional impairment is *already* apparent (16, 17, 109, 141, 178); with screening criteria to detect 'risk' of developing malnutrition (141, 158, 178) identical to that used to diagnose malnutrition (135, 140, 145).

Older adults with cancer are at high risk of each of these conditions, with well-known risk factors. For example, cancers affecting the gastrointestinal tract, diseases that increase resting energy expenditure e.g., from pulmonary insufficiency (lung cancer, chronic obstructive pulmonary disease), or those who are older, hospitalised, or in long-term care, known to be at high risk of malnutrition

(12, 155, 172), similarly those with gastric, head and neck, pancreatic, or lung cancers at high risk of cachexia (27), and those who are older, physically inactive, and long-term care at risk of developing sarcopenia (541, 542).

Therefore, we already have the ability to predict who is at risk of developing these conditions. This, alongside the use of early-warning signs for these conditions (such as anorexia, insulin resistance, and/or raised inflammatory markers in cachexia (19, 23)), could be used to trigger initiation of interventions, rather than waiting until nutritional and physical function problems have already occurred.

Prehabilitation, of improving a patient's general health and physical wellbeing prior to a medical intervention (543), is associated with improved patient outcomes, including improved exercise tolerance, reduced treatment anxiety, and reduced length of hospital stay (544). There is emerging evidence regarding the benefits and feasibility of prehabilitation in medical oncology, before the initiation of oncological treatments (544, 545). The requirement to identify and manage nutritional and physical function problems *before* they become a threat to a patient's health and treatment, encompasses the process of prehabilitation, by acting on, and implementing interventions at the first sign of deterioration, rather than waiting until problems have developed.

Screening for these conditions in a way that detects those most at risk of pre-cachexia, 'pre'-sarcopenia, or 'pre'-malnutrition, by taking into account factors such as a patient diagnosis (to highlight the highest risk patients), or warning predictor variables, such as reduced appetite, may help prevent the development or severity of these conditions, and allow tailored interventions to be delivered to manage the conditions – preventing or minimising deterioration of nutrition and physical function.

The ethics of screening must also be considered, as discussed in section 5.6, criteria for screening programmes include the requirement to identify conditions at a stage when an effective treatments can be offered (402), with the benefit of screening and identifying the condition weighed against the possible harms (402, 427).

This adds emphasis to the need to shift the focus of screening, and of the markers of the three conditions used, away from established nutritional and physical function signs and symptoms, and towards early warning signs for the conditions. As, identification of established conditions, rather than 'pre'- conditions, limits the number of effective treatments available.

However, with some conditions, such as refractory cachexia, even though no effective strategies for reversing the condition exist (19, 28, 402), diagnosing the condition would allow for a focus on

quality of life, symptom management, provision of information to families and patients, and prevention of inappropriate interventions, such as aggressive nutritional support.

10.4 Key predictor variables and streamlined screening methods

The results of the regression analyses and qualitative interviews from my mixed-methods study support my systematic review findings (**Chapter Four**) regarding markers of malnutrition in older adults with cancer; reduced food intake and visual appearance are predictors of malnutrition. Findings from the qualitative interviews suggest visual changes are strong signals when it comes to patients self-identifying problems with their nutrition and physical function, more so than other more commonly used markers, such as objective measures of weight loss, which were reportedly infrequently checked by patients.

Visual changes were also noticeable to patients' families, with prompts for concern often initiated by family. Interestingly, slow declines in weight, or gradual reductions in physical function, were not perceived as concerning, it was only when either rapid changes occurred, or nutrition and function had deteriorated to a point of impacting cancer treatment and care, that concerns were provoked. As well as being clinically significant, key predictor variables must have face- and content-validity, and be clinically relevant (63, 198); with visual markers of change both clinically relevant, and have face validity with patients. My review (**Chapter Five**) identified no studies investigating family or carers' views of malnutrition screening, identifying a need to explore their perceptions, and at what point visual changes become a concern.

Body mass index is a commonly used marker for malnutrition, with my systematic review (**Chapter Four**) finding that a very low body mass index (<18kg/m^2) was associated with poorer clinical outcomes (221). Many nutritional screening tools use body mass index to identify risk of malnutrition (**Table 17**), including frequently used tools such as MUST (158) and the NRS-2002 (180), with body mass index used in most malnutrition diagnostic criteria e.g., NICE (138), ESPEN consensus statement (140) (**Table 18**). However, body mass index in itself is a single measure used to categorise adults based upon their estimated 'fatness' (546, 547). Body mass index does not show changes in body weight or composition, cannot be used in isolation as an indicator of nutritional status over time, and has repeatedly been shown to be a poor indicator of fat mass (546, 547). Large-scale studies and meta-analyses suggest that higher body mass indexes are associated with all-cause and cancer-specific mortality (548, 549).

However, studies often look at the association of higher body mass index with disease risk, and do not consider the impact of body mass index on survival during cancer diagnosis and treatment. A pooled analysis of 22 clinical trials (n=11,724) looking at body mass index at the time of cancer

diagnosis and survival in multiple cancer types and stages found inconsistent associations between body mass index and survival, with differences seen in mortality and body mass index based on sex, specific cancer diagnosis, and cancer stage (550). Although very low body weight may be predictive of poor outcomes, possibly related to emaciation, my findings highlight the usefulness of changing appearances rather than single point-in-time measures, and do not support the use of body mass index in assessing malnutrition in isolation.

In this thesis I aimed to determine the feasibility of distinguishing between elements of malnutrition, sarcopenia, and cachexia in older adults with cancer. As previously discussed, key predictor variables were highlighted by the quantitative analysis (**Table 40**), with arguments made regarding the assessment of inflammation, appetite, visual appearance, meal consumption, rapid weight loss, and frailty to differentiate between conditions. This, however, contradicts recent consensus malnutrition diagnostic criteria; the GLIM criteria (145) published in 2019, aimed to build a global core diagnostic criterion for malnutrition, using phenotypic metrics for grading severity, and etiologic criteria to guide interventions. However, the GLIM criteria for malnutrition include screening methods and criteria for sarcopenia and cachexia *within* their diagnostic criteria for malnutrition (145). As I have discussed, the delineation and differentiation of malnutrition from sarcopenia and cachexia, to allow condition-specific treatment and management is required. However, the overlapping of the three conditions by the GLIM criteria (145) hinders this, by 'tarring' all nutrition-related wasting disorders with one brush, under malnutrition, thereby contradictory to calls to distinguish between the conditions (18, 23, 61).

10.4.1 Feasibility and utility of screening

Although these conditions are highly prevalent in this group of older adults with cancer, and this thesis suggests feasibility of screening for the conditions, several barriers to addressing the conditions were identified. My findings demonstrate that these conditions are misunderstood and overlooked by patients, with the clinical management of other comorbidities overshadowing nutritional and physical function concerns. This is compounded by a low perception of risk of these conditions by patients, and a perceived disregard of these conditions by clinicians. These factors result in nutritional and physical function problems being discounted whilst also being seen as inevitable, despite conflicting beliefs that past health behaviours are protective against these problems. These barriers, alongside others identified, which include; i) lack of personalised information or advice, ii) timing of interventions and screening, iii) fear of causing harm by engaging in physical activity, iv) self-assurance of perceived current health, and v) lack of encouragement from medical staff, mean that nutritional and physical function concerns remained unidentified and unmanaged in older adults with cancer, despite a high prevalence and substantial impact of the

conditions on patient's health and quality of life. The findings of my mixed-methods study corroborate the findings of my systematic review of patients' experiences (551) (**Chapter Five**), where weight loss was often viewed as categorically positive, where 'healthy' diets high in fruits and vegetables were pursued, and 'malnutrition' was viewed as a personal impossibility.

Similarly, this finding, of a view of the need to follow a 'healthy diet' was seen in **Chapter Five**, in which only high-income countries were studied, and was also seen in the mixed-methods study. Public health messages in higher-income countries often have a focus on managing non-communicable disease burdens, such as cardiovascular diseases, obesity, diabetes, and cancer screening, with a focus on improving diet quality and physical activity (552). In lower-income countries, a focus on the management of child undernutrition, and communicable diseases, such as tuberculosis, is more prevalent (552). It may be this prevailing public health message, of (over)weight management, and achieving a balanced diet (553), which is the source of some of the dissonance in nutrition perceptions expressed by the participants, and results in malnutrition being overlooked in, and ignored by, this population. These barriers; of patients' perceptions of the conditions, alongside clinicians' perceptions and perceived reticence, must be addressed to enable successful management of these common problems in older adults with cancer. Although **Chapter Five** included other diagnoses, and a wider range of participant ages, concordance was seen with my qualitative interview findings, with interview findings expanding upon the why and interrelationship of themes identified in **Chapter Five**. This may suggest findings from my interviews may translate into other areas of health.

Finally, as discussed in section **10.3**, the suggested markers for malnutrition, sarcopenia, and cachexia identified in this thesis, and those currently used in screening tools, identify *established* nutritional or physical deterioration. As discussed, older adults with cancer, particularly those with cancers affecting the gastrointestinal tract or respiratory system, are known to be at high risk of developing these conditions, regardless of their current nutritional or physical function status.

Markers identified in this thesis may be used to streamline current screening methods to detect established malnutrition, sarcopenia, and cachexia, but further research is required to determine the feasibility and utility of screening for 'pre' conditions. As suggested with pre-cachexia, early signs, such as small unintentional weight loss, anorexia, impaired glucose tolerance, or inflammation, indicate an onset of the condition (19, 23). Further research is required to develop equivalent criteria for 'pre-malnutrition' and 'pre-sarcopenia', with results of this thesis potentially suggesting onset of frailty or reducing physical function, and reduced oral intake are important markers of early nutritional and physical function decline.

10.5 Addressing the overall thesis aim

The overall aim of this thesis was to understand better the prevalence, detection, assessment, and patients' experiences of malnutrition, sarcopenia, and cachexia in older adults with cancer.

My thesis has generated several novel findings;

Malnutrition, sarcopenia, and cachexia are highly prevalent, overlapping conditions in this population of older adults with cancer. However, overlapping mandatory criterion, such as >5% weight loss or functional decline, mean current screening tools only identify the conditions once they are established and more difficult to address, rather than identifying the risk of them developing.

There is a fundamental misunderstanding of the causes and consequences of poor nutrition and physical function by patients. Patients hold conflicting views, often at the same time, regarding the assumed inevitability of these problems, whilst also minimising their personal risk (it won't happen to me).

Minimisation of the risk of these problems is confirmed by a perceived lack of importance afforded to the topics by clinicians. Overshadowing of the conditions, combined with a low perception of self-risk, and their assumed inevitability, meant problems were ignored until weight loss hit a critical tipping point, such as becoming rapid, visible to family, or threatening fitness for cancer treatments.

Screening is acceptable, however, changes to the criterion, to identify *risk*, rather than established symptoms, are required. Routine screening for the three conditions, with identification of longitudinal changes in weight, nutrition, and function, is essential. My findings support the notion of a simplified screening tool that includes; assessment of visual changes (physical appearance and diet quantity), frailty, and causes of weight loss and inflammation, to allow identification and differentiation of the three conditions, with early indicators of the conditions e.g., anorexia in the absence of weight loss for cachexia, prioritised to allow interventions to be implemented earlier. Future work investigating predictor variables for pre-sarcopenia, and pre-malnutrition, in addition to pre-cachexia, is needed to address these anticipated problems *before* they cause complications.

Screening presents an opportunity to address overshadowing and misconceptions, with benefits of screening including; the opportunity to raise concerns, consider issues, provide reassurance, and in some incidences, act as an intervention in itself by providing assurances and encouragement to complete basic physical activities. However, barriers to screening were also highlighted that must be considered when moving forward. In particular, addressing the perceived detachment of the relationship between nutrition and physical function, consideration of the timing of screening in a

patient's journey, addressing patients' pre-existing perceptions of these conditions, and the role of clinicians in raising and addressing patient concerns regarding their nutrition, weight and physical function.

10.6 Strengths and limitations

The strengths and limitations of each research method used in this thesis are discussed in **Chapter Three**. One of the main strengths of this thesis is the use of the mixed-methods approach, with the addition of systematic reviews (again, using mixed-methods) to comprehensively examine the current evidence base. The use of multiple methods of data collection allows triangulation of data, and integration of findings to gain a richer understanding of this topic (191, 192).

In particular, this approach allowed increased confidence in conclusions gained from the quantitative aspects of the mixed-methods study, despite the reduced sample size caused by difficulties in recruitment during the pandemic. The uncertainty arising from the small sample size is seen in the wide confidence intervals in some of the statistical test results. However, quantitative findings, such as the use of visual markers in malnutrition, are supported by findings from the qualitative research, and provide an insight into 'why', which would not have been achieved through quantitative data collection alone. Additionally, completion of the systematic review of patients' experiences of nutritional screening provided a stepping stone to allow more focused qualitative interviews in the mixed-methods study and a platform on which to base the initial topic guide. Despite a smaller qualitative sample size than initially targeted, depth of knowledge and rich data were still achieved, and the review findings allowed exploration of the relationships of interlinking themes and feedback loops, which may not have been achievable if more time were spent exploring the findings already gained from the review.

The use of concurrent data collection for qualitative interviews and quantitative data allowed detailed exploration of participants' views and experiences of the screening process, with interviews conducted soon after screening, which allowed recent recall of the process.

Older adults with cancer, particularly those with metastatic or late-stage disease, can be a difficult to reach population for research. However, recruitment rates achieved were satisfactory, with a substantial number of patients with advanced disease consenting to participation in the study. This, alongside researching an understudied, and as seen, often overlooked topic, meant my research has been able to provide a voice for this overlooked, but extensive group – of older adults with cancer and nutrition-related wasting disorders.

However, there are several limitations of this research. In addition to the imposed study limitations, as discussed in section **3.7**, other limitations relating to the influence of the COVID-19 pandemic upon the study data collection and analysis, may have impacted study findings. The pandemic disrupted several aspects of this thesis, most predominantly the mixed-methods study; resulting in reduced study sample sizes and an inability to complete certain planned aspects of the study e.g., clinician interviews of a refined tool. The impact of the pandemic, and mitigation factors employed, are discussed in section **6.7**.

The complexities of these conditions; of both their high prevalence, under-researched nature, and substantial overlap, in patients who are experiencing other comorbidities, has made addressing this topic challenging. In particular, approaching and consenting individuals with a high disease burden, with difficulties in recruiting from outpatients. As discussed, engagement of outpatient members of staff, and integration of the researcher into outpatient clinics, may aid recruitment in similar future studies. Additionally, engagement of potential patient participants in a topic that is often overlooked, or not seen as a priority, presented challenges; with potential participants declining involvement as the study topic was not of interest, or was perceived as not relevant to themselves.

Further, as the sole researcher, for both data collection and analysis, and as a dietitian, my work is at risk of bias. Although mitigating factors were employed, such as acknowledgement of this bias, see section **6.6.6**, reflexivity, an objective and pragmatic stance, involvement of other researchers in data analysis, and data analysis methods aimed to prevent bias e.g., systematic literature searching, following thematic analysis methods for qualitative analysis, this risk will remain.

Another limitation of this thesis was the study population, recruited from a single site, focusing on six specific groups of cancer, making the generalisability of these results limited. However, as findings from the more diverse study populations in the systematic reviews support several findings of the mixed-methods study, with the study expanding upon these, it does support commonalities and applicable findings.

Further, target qualitative sample sizes were based on information power (301). As the topic explored in the interviews was narrow, will all participants having experiences of screening, and views on nutrition and function, this meant data quality was rich, and allowed additional analysis using feedback loops, and compensated for the smaller than targeted sample size.

10.7 Clinical implications

Greater acknowledgement and prioritisation of malnutrition, sarcopenia, and cachexia by health care professionals is required when treating older adults with cancer. Disruption of the negative cycle of nutritional and functional problems being misattributed to other health conditions, or seen as a normal, and therefore accepted part of cancer, ageing, or other comorbidities, resulting in the problems being ignored, despite their negative impact upon patients, is required; initiated by clinicians, including doctors, signalling the importance of this aspect of care. My findings suggest screening methods to identify and differentiate between malnutrition and cachexia in older adults with cancer, but require testing with a larger sample. However, increased education regarding the three conditions, the inclusion of basic functional assessments in clinical assessment, and acknowledgement that weight loss may not be caused by malnutrition alone in this population group, are easily implementable first steps.

Dietitians are a key resource for the treatment of malnutrition in the NHS, however, screening for cachexia and sarcopenia are not part of routine dietetic assessments. The results of this study show the overlap of, and difficulty distinguishing between the three conditions, particularly when only using basic anthropometric measures e.g., weight, hand-grip strength. Increasing knowledge of the conditions and their predictor variables would help prevent the blanket treatment of nutrition-related wasting disorders with high-calorie, high-protein advice, which may not be beneficial, can be costly to the NHS, and in some cases may cause distress if not effective in managing weight loss. Additionally, the inclusion of functional assessments in dietetic assessments would also present an opportunity to address the relationship between nutrition and physical function; which is prioritised among this patient group, and may improve adherence to nutritional advice.

However, due to current limited dietetic staffing – which is not prioritised by commissioners – the role of other front-facing practitioners, and their knowledge of the causes and consequences of these conditions, as well as the potential benefits if these conditions are managed early enough, must be addressed. Increased education of the 'early warning signs' for these conditions, alongside *who* is at risk, and what basic advice can be provided to stem nutritional and physical function problems *before* progressive symptoms appear and anticancer treatments are impacted, is required. However, this would include changing health care professionals' perceptions of nutritional and physical function problems in cancer, to high importance, proactive prevention, e.g., addressing at the start of treatment, rather than current practices of providing inappropriate generic advice or worse, ignoring the problems. Further, a change in clinical management, away from individual therapies, and towards a more holistic, multi-disciplinary approach, to aid in their management is required; with inclusion of physiotherapists and occupational therapists to aid with mobility and

physical function, dietitians for nutrition, doctors in the management of inflammation, and nursing and support staff in the provision of appropriate baseline advice to aid in the prevention of these conditions.

10.8 Research implications

This research has shown that malnutrition, sarcopenia, and cachexia are highly prevalent conditions in older adults with cancer, which have detrimental effects on patients' anticancer treatments and quality of life. Despite this, these conditions are often overlooked, or ignored until they have already impacted upon patient wellbeing. Screening tools used for the three conditions identify established symptoms, such as weight loss or loss of function. Future work is required to adapt current screening tools to instead identify *risk* of developing these conditions, with a focus on signs, symptoms and clinical characteristics that predict the risk, rather than acknowledge the presence, of the conditions.

As shown, there is a significant overlap between malnutrition and cachexia in this population. However, differentiating between protein-energy malnutrition and cachexia, in non-cachexic patients, is not currently possible using current screening tools due to the overlapping diagnostic criteria, and, in particular, the reliance on percentage weight loss to diagnose both conditions. This prevents tailored interventions to manage the conditions. In addition, the impact of COVID-19 on these conditions, and upon their detection, assessment, and treatment, is required. Going forward, COVID-19 will continue to affect cancer care, and patients' risk of malnutrition, sarcopenia, and cachexia for years to come (457, 461, 463). Therefore, work is required to determine the relationship between the three conditions and COVID-19, and COVID-19's impact on patient outcomes, to determine how these findings translate into a world where COVID-19 remains endemic.

These questions could be addressed in a larger, multi-site longitudinal study. Future studies should include a wider range of cancer diagnoses, and include both inpatients and outpatients. These factors would allow for greater generalisability of findings, allow for multivariate analysis of predictor variables, and allow assessment of confounding variables and relationships with longitudinal outcomes, as was initially planned. Further investigation into predictor variables of the conditions, and the validity (face and content validity, and clinical utility) of the predictor variables identified in this thesis, could be achieved through longitudinal follow-up of cancer patients. This could allow identification of pre-condition markers, and could be used to develop and refine current screening tools to identify 'pre-' malnutrition, 'pre'-sarcopenia, and pre- cachexia in older adults with cancer.

As identified in the systematic review of malnutrition markers, there is considerable heterogeneity in markers for malnutrition and their thresholds, with outcomes mainly focusing on clinical outcomes,

with the results of the mixed-methods study indicating alternate outcomes, such as visual weight loss or dietary intake, being more relevant and useful to patients. This shows a need for a standardised patient-centred outcome list. This would enable comparison of intervention effectiveness, and may improve patient engagement (with more patient-relevant outcomes), and aid acceptance and uptake of nutritional and physical function advice by older adults with cancer.

Future research, investigating patient, family, carers, and clinicians' perceptions of the three conditions is also required. Results of this thesis show these conditions are overlooked, perceived as normal, inevitable, or minor. Results of the mixed-methods study highlighted a dissonance in patients' views regarding their perceptions of the conditions. How this dissonance is managed by patients, and how to address this to improve recognition and increase prioritisation of these conditions, requires investigation. Patients perceived clinicians to be overlooking or ignoring their nutritional or physical function concerns, with evidence of these conditions being viewed as 'secondary concerns', also seen. How to change clinicians' perspectives of these conditions, and address 'forgotten symptoms', in this case, weight loss, reduced mobility, and others such as breathlessness and fatigue, requires future work. This includes research into *how* to discuss nutritional and physical function problems, when little may be achieved in stemming weight loss or functional decline. Clinician interviews were planned as part of this thesis but not completed, as previously discussed. Exploration of clinicians' perceptions of these conditions, their roles in their identification and management, and investigations into how to improve recognition of these conditions in clinical practice would also be beneficial for the management of malnutrition, sarcopenia, and cachexia in older adults with cancer.

This thesis also highlighted the difficulties caused by a misunderstanding of the terminology used around malnutrition, sarcopenia, and cachexia. The terms 'malnutrition', 'sarcopenia', and 'cachexia' are not understood by patients, and although 'nutrition problems' and 'function' are more readily comprehended, these did not always impart the potential seriousness of the conditions. Alongside this, the impact of generic public health messages (and the overriding message to lose weight) upon patients' perceptions of their own health, and upon their understanding of the conditions, as well as upon the required alternations to diet needed during anticancer treatment, were seen. Research into language used, and how to modify public health messages, to prevent these misunderstandings, is needed.

10.9 Summary

In this thesis, I have presented the results of a systematic review of malnutrition markers in older adults with cancer, finding three markers of malnutrition with evidence of impact on patient outcomes, however, the appropriateness of 'proxy' markers in assessing nutritional status required deliberation, particularly with the overlapping definitions and diagnostic criteria of other nutrition-related wasting disorders. A second systematic review, investigating patient, family, and carers' views and experiences of malnutrition screening, found no studies investigating family or carer views, and suggested that although screening was seen as 'acceptable', a lack of understanding of the causes and consequences of malnutrition resulted in disregard of screening results and associated advice. My mixed-methods study found a high prevalence, and substantial overlap of the three conditions in my group of older adults with cancer.

Despite the high prevalence of the conditions, nutritional and functional problems were often overlooked, overshadowed, misunderstood, and both seen as personally-impossible yet inevitable. Findings highlight the need to change our perceptions and management of these conditions, of identifying those truly 'at risk', rather than those who have already developed the conditions, and a need to alter perceptions of these conditions, with a focus on *how* to manage these conditions *before* they cause morbidity, rather than disregarding them, with a need to implement interventions before it becomes too late.

References

1. World Cancer Report. Lyon: International Agency for Research on Cancer 2014.
2. Estapé T. Cancer in the Elderly: Challenges and Barriers. Asia Pac J Oncol Nurs. 2018;5(1):40-2.
3. Marosi C, Köller M. Challenge of cancer in the elderly. ESMO Open. 2016;1(3):e000020.
4. Cancer Research UK. Cancer mortality by age. Online 2019 [7th July 2019]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/age#heading-Three.
5. Owusu C, Berger NA. Comprehensive geriatric assessment in the older cancer patient: coming of age in clinical cancer care. Clin Pract (Lond). 2014;11(6):749-62.
6. Butterworth CE. The skeleton in the hospital closet. Nutrition Today. 1974;9(2):4-8.
7. Walsh D, Szafranski M, Aktas A, Kadakia KC. Malnutrition in Cancer Care: Time to Address the Elephant in the Room. Journal of oncology practice. 2019:Jop1900165.
8. Caillet P, Liuu E, Raynaud Simon A, Bonnefoy M, Guerin O, Berrut G, et al. Association between cachexia, chemotherapy and outcomes in older cancer patients: A systematic review. Clinical nutrition (Edinburgh, Scotland). 2017;36(6):1473-82.
9. Kim JW, Kim YJ, Lee K-W, Chang H, Lee J-O, Kim K-I, et al. The early discontinuation of palliative chemotherapy in older patients with cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2014;22(3):773-81.
10. Cousin S, Hollebecque A, Koscielny S, Mir O, Varga A, Baracos VE, et al. Low skeletal muscle is associated with toxicity in patients included in phase I trials. Investigational new drugs. 2014;32(2):382-7.
11. Zhang X, Tang T, Pang L, Sharma SV, Li R, Nyitray AG, et al. Malnutrition and overall survival in older adults with cancer: A systematic review and meta-analysis. J Geriatr Oncol. 2019.
12. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr. 2017;36(5):1187-96.
13. Peterson SJ, Mozer M. Differentiating Sarcopenia and Cachexia Among Patients With Cancer. Nutr Clin Pract. 2017;32(1):30-9.
14. National Institute for Health and Clinical Excellence. Nutrition Support in Adults: Quality Standard SQ24. Newcastle: NICE; 2012.
15. Ye XJ, Ji YB, Ma BW, Huang DD, Chen WZ, Pan ZY, et al. Comparison of three common nutritional screening tools with the new European Society for Clinical Nutrition and Metabolism (ESPEN) criteria for malnutrition among patients with geriatric gastrointestinal cancer: a prospective study in China. BMJ Open. 2018;8(4):e019750.
16. Argiles JM, Betancourt A, Guardia-Olmos J, Pero-Cebollero M, Lopez-Soriano FJ, Madeddu C, et al. Validation of the CAchexia SCOre (CASCO). Staging Cancer Patients: The Use of miniCASCO as a Simplified Tool. Front Physiol. 2017;8:92.
17. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.
18. 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. 2018;108(6):1196-208.
19. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology. 2011;12(5):489-95.
20. Fearon KC, Voss AC, Hustead DS, Cancer Cachexia Study G. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. The American journal of clinical nutrition. 2006;83(6):1345-50.
21. Argiles JM, Moore-Carrasco R, Fuster G, Busquets S, Lopez-Soriano FJ. Cancer cachexia: the molecular mechanisms. The international journal of biochemistry & cell biology. 2003;35(4):405-9.

22. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr. 2008;27(6):793-9.
23. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clinical nutrition (Edinburgh, Scotland). 2010;29(2):154-9.
24. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015;33(1):90-9.
25. Vanhoutte G, van de Wiel M, Wouters K, Sels M, Bartolomeeussen L, De Keersmaecker S, et al. Cachexia in cancer: what is in the definition? BMJ open gastroenterology. 2016;3(1):e000097.
26. Wesseltoft-Rao N, Hjermstad MJ, Ikdahl T, Dajani O, Ulven SM, Iversen PO, et al. Comparing two classifications of cancer cachexia and their association with survival in patients with unresected pancreatic cancer. Nutr Cancer. 2015;67(3):472-80.
27. Anker MS, Holcomb R, Muscaritoli M, von Haehling S, Haverkamp W, Jatoi A, et al. Orphan disease status of cancer cachexia in the USA and in the European Union: a systematic review. J Cachexia Sarcopenia Muscle. 2019;10(1):22-34.
28. Aoyagi T, Terracina KP, Raza A, Matsubara H, Takabe K. Cancer cachexia, mechanism and treatment. World J Gastrointest Oncol. 2015;7(4):17-29.
29. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr. 2006;83(4):735-43.
30. Van Lancker A, Velghe A, Van Hecke A, Verbrugghe M, Van Den Noortgate N, Grypdonck M, et al. Prevalence of Symptoms in Older Cancer Patients Receiving Palliative Care: A Systematic Review and Meta-Analysis. Journal of Pain and Symptom Management. 2014;47(1):90-104.
31. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. Lancet (London, England). 2003;362(9384):640-50.
32. Kurzrock R. Kurzrock RThe role of cytokines in cancer-related fatigue. Cancer 92: 1684-1688. Cancer. 2001;92:1684-8.
33. Patton R, Paval DR, McDonald JJ, Brown D, Gallagher IJ, Skipworth RJE, et al. Relationship between cytokines and symptoms in people with incurable cancer: A systematic review. Critical Reviews in Oncology/Hematology. 2021;159:103222.
34. Lai S. Cancer related fatigue and cancer cachexia are the consequence of endocrine failure caused by persistent stress. Medical Hypotheses. 2019;123:60-2.
35. Ezeoke CC, Morley JE. Pathophysiology of anorexia in the cancer cachexia syndrome. Journal of cachexia, sarcopenia and muscle. 2015;6(4):287-302.
36. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nature reviews Cancer. 2014;14(11):754-62.
37. Skipworth RJ, Fearon KC. The scientific rationale for optimizing nutritional support in cancer. Eur J Gastroenterol Hepatol. 2007;19(5):371-7.
38. McClement S. Cancer anorexia-cachexia syndrome: psychological effect on the patient and family. Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society. 2005;32(4):264-8.
39. Hinsley R, Hughes R. The reflections you get: an exploration of body image and cachexia. International journal of palliative nursing. 2007;13:84-9.
40. Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer. 2008;44(8):1124-32.
41. Hopkinson JB. Psychosocial impact of cancer cachexia. J Cachexia Sarcopenia Muscle. 2014;5(2):89-94.
42. Rhondali W, Chisholm GB, Daneshmand M, Allo J, Kang DH, Filbet M, et al. Association between body image dissatisfaction and weight loss among patients with advanced cancer and their caregivers: a preliminary report. J Pain Symptom Manage. 2013;45(6):1039-49.

43. Loumaye A, Thissen J-P. Biomarkers of cancer cachexia. Clinical Biochemistry. 2017;50(18):1281-8.
44. Coletti D. Chemotherapy-induced muscle wasting: an update. Eur J Transl Myol. 2018;28(2):7587-.
45. Kalantar-Zadeh K, Rhee C, Sim JJ, Stenvinkel P, Anker SD, Kovesdy CP. Why cachexia kills: examining the causality of poor outcomes in wasting conditions. Journal of cachexia, sarcopenia and muscle. 2013;4(2):89-94.
46. Schmidt SF, Rohm M, Herzig S, Berriel Diaz M. Cancer Cachexia: More Than Skeletal Muscle Wasting. Trends in cancer. 2018;4(12):849-60.
47. Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines(☆). ESMO Open. 2021;6(3):100092.
48. Roeland EJ, Bohlke K, Baracos VE, Bruera E, Del Fabbro E, Dixon S, et al. Management of Cancer Cachexia: ASCO Guideline. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(21):2438-53.
49. Currow D, Temel JS, Abernethy A, Milanowski J, Friend J, Fearon KC. ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small-cell lung cancer (NSCLC) patients with cachexia. Ann Oncol. 2017;28(8):1949-56.
50. Crawford J, Prado CMM, Johnston MA, Gralla RJ, Taylor RP, Hancock ML, et al. Study Design and Rationale for the Phase 3 Clinical Development Program of Enobosarm, a Selective Androgen Receptor Modulator, for the Prevention and Treatment of Muscle Wasting in Cancer Patients (POWER Trials). Curr Oncol Rep. 2016;18(6):37-.
51. Baldwin C, Spiro A, McGough C, Norman AR, Gillbanks A, Thomas K, et al. Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2011;24(5):431-40.
52. Sadeghi M, Keshavarz-Fathi M, Baracos V, Arends J, Mahmoudi M, Rezaei N. Cancer cachexia: Diagnosis, assessment, and treatment. Critical Reviews in Oncology/Hematology. 2018;127:91-104.
53. Argiles JM, Busquets S, Lopez-Soriano FJ, Costelli P, Penna F. Are there any benefits of exercise training in cancer cachexia? J Cachexia Sarcopenia Muscle. 2012;3(2):73-6.
54. Argilés JM, López-Soriano FJ, Toledo M, Betancourt A, Serpe R, Busquets S. The cachexia score (CASCO): a new tool for staging cachectic cancer patients. Journal of cachexia, sarcopenia and muscle. 2011;2(2):87-93.
55. Zhou T, Wang B, Liu H, Yang K, Thapa S, Zhang H, et al. Development and validation of a clinically applicable score to classify cachexia stages in advanced cancer patients. Journal of cachexia, sarcopenia and muscle. 2018;9(2):306-14.
56. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000;89(7):1634-46.
57. Ribaudo JM, Cella D, Hahn EA, Lloyd SR, Tchekmedyian NS, Von Roenn J, et al. Re-validation and shortening of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2000;9(10):1137-46.
58. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982;5(6):649-55.
59. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing. 2010;39(4):412-23.

60. Blum D, Stene GB, Solheim TS, Fayers P, Hjermstad MJ, Baracos VE, et al. Validation of the Consensus-Definition for Cancer Cachexia and evaluation of a classification model--a study based on data from an international multicentre project (EPCRC-CSA). Ann Oncol. 2014;25(8):1635-42.
61. Rolland Y, Abellan van Kan G, Gillette-Guyonnet S, Vellas B. Cachexia versus sarcopenia. Current opinion in clinical nutrition and metabolic care. 2011;14(1):15-21.
62. Elia M. Defining, Recognizing, and Reporting Malnutrition. The international journal of lower extremity wounds. 2017;16(4):230-7.
63. Salkind NJ. Encyclopedia of Research Design. 2010.
64. Rosenberg IH. Summary comments. The American journal of clinical nutrition. 1989;50(5):1231-3.
65. Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: two sides of the same coin. Front Aging Neurosci. 2014;6:192-.
66. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2006;61(10):1059-64.
67. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011;12(4):249-56.
68. Newman AB, Kupelian V, Visser M, Simonsick E, Goodpaster B, Nevitt M, et al. Sarcopenia: alternative definitions and associations with lower extremity function. J Am Geriatr Soc. 2003;51(11):1602-9.
69. Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc. 2011;12(6):403-9.
70. Chen L-K, Liu L-K, Woo J, Assantachai P, Auyeung T-W, Bahyah KS, et al. Sarcopenia in Asia: Consensus Report of the Asian Working Group for Sarcopenia. Journal of the American Medical Directors Association. 2014;15(2):95-101.
71. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014;69(5):547-58.
72. Dam TT, Peters KW, Fragala M, Cawthon PM, Harris TB, McLean R, et al. An evidence-based comparison of operational criteria for the presence of sarcopenia. J Gerontol A Biol Sci Med Sci. 2014;69(5):584-90.
73. Fernandes LV, Paiva AEG, Silva ACB, de Castro IC, Santiago AF, de Oliveira EP, et al. Prevalence of sarcopenia according to EWGSOP1 and EWGSOP2 in older adults and their associations with unfavorable health outcomes: a systematic review. Aging clinical and experimental research. 2021.
74. Bozzetti F, Cozzaglio L, Biganzoli E, Chiavenna G, De Cicco M, Donati D, et al. Quality of life and length of survival in advanced cancer patients on home parenteral nutrition. Clinical nutrition (Edinburgh, Scotland). 2002;21(4):281-8.
75. Shafiee G, Keshtkar A, Soltani A, Ahadi Z, Larijani B, Heshmat R. Prevalence of sarcopenia in the world: a systematic review and meta- analysis of general population studies. Journal of diabetes and metabolic disorders. 2017;16:21.
76. Cruz-Jentoft AJ, Landi F, Schneider SM, Zuniga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing. 2014;43(6):748-59.
77. Pamoukdjian F, Bouillet T, Levy V, Soussan M, Zelek L, Paillaud E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. Clin Nutr. 2018;37(4):1101-13.
78. Riuzzi F, Sorci G, Sagheddu R, Chiappalupi S, Salvadori L, Donato R. RAGE in the pathophysiology of skeletal muscle. Journal of cachexia, sarcopenia and muscle. 2018;9(7):1213-34.

79. Gonzalez-Freire M, de Cabo R, Studenski SA, Ferrucci L. The Neuromuscular Junction: Aging at the Crossroad between Nerves and Muscle. Front Aging Neurosci. 2014;6:208-.
80. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. The Lancet. 2019;393(10191):2636-46.
81. Kim TN, Choi KM. Sarcopenia: definition, epidemiology, and pathophysiology. Journal of bone metabolism. 2013;20(1):1-10.
82. Liguori I, Russo G, Aran L, Bulli G, Curcio F, Della-Morte D, et al. Sarcopenia: assessment of disease burden and strategies to improve outcomes. Clin Interv Aging. 2018;13:913-27.
83. Landi F, Calvani R, Tosato M, Martone AM, Ortolani E, Savera G, et al. Anorexia of Aging: Risk Factors, Consequences, and Potential Treatments. Nutrients. 2016;8(2):69-.
84. Gariballa S, Alessa A. Sarcopenia: prevalence and prognostic significance in hospitalized patients. Clin Nutr. 2013;32(5):772-6.
85. Cosqueric G, Sebag A, Ducolombier C, Thomas C, Piette F, Weill-Engerer S. Sarcopenia is predictive of nosocomial infection in care of the elderly. Br J Nutr. 2006;96(5):895-901.
86. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. J Am Geriatr Soc. 2004;52(1):80-5.
87. TheKingsFund. The NHS budget and how it has changed Online 2019 [cited 2019 09 September]. Available from: https://www.kingsfund.org.uk/projects/nhs-in-a-nutshell/nhs-budget.
88. Otten L, Stobaus N, Franz K, Genton L, Muller-Werdan U, Wirth R, et al. Impact of sarcopenia on 1-year mortality in older patients with cancer. Age and Ageing. 2019;48(3):413-8.
89. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009;15(22):6973-9.
90. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. European Journal of Cancer. 2016;57:58-67.
91. Ansari E, Chargi N, van Gemert JTM, van Es RJJ, Dieleman FJ, Rosenberg A, et al. Low skeletal muscle mass is a strong predictive factor for surgical complications and a prognostic factor in oral cancer patients undergoing mandibular reconstruction with a free fibula flap. Oral Oncol. 2019;101:104530.
92. Cipolli GC, Yassuda MS, Aprahamian I. Sarcopenia Is Associated with Cognitive Impairment in Older Adults: A Systematic Review and Meta-Analysis. Journal of Nutrition Health & Aging. 2019;23(6):525-31.
93. Cesari M, Rolland Y, Abellan Van Kan G, Bandinelli S, Vellas B, Ferrucci L. Sarcopenia-related parameters and incident disability in older persons: results from the "invecchiare in Chianti" study. The journals of gerontology Series A, Biological sciences and medical sciences. 2015;70(4):457-63.
94. JafariNasabian P, Inglis JE, Reilly W, Kelly OJ, Ilich JZ. Aging human body: changes in bone, muscle and body fat with consequent changes in nutrient intake. J Endocrinol. 2017;234(1):R37-r51.
95. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019;393(10191):2636-46.
96. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57(1):6-14.
97. Fulop T, Jr., Worum I, Csongor J, Foris G, Leovey A. Body composition in elderly people. I. Determination of body composition by multiisotope method and the elimination kinetics of these isotopes in healthy elderly subjects. Gerontology. 1985;31(1):6-14.
98. Ali R, Baracos VE, Sawyer MB, Bianchi L, Roberts S, Assenat E, et al. Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. Cancer Med. 2016;5(4):607-16.
99. Hirsch L, Bellesoeur A, Boudou-Rouquette P, Arrondeau J, Thomas-Schoemann A, Kirchgesner J, et al. The impact of body composition parameters on severe toxicity of nivolumab. Eur J Cancer. 2020;124:170-7.

100. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-47.
101. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev. 2009;41(2):67-76.
102. Dent E, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, et al. International Clinical Practice Guidelines for Sarcopenia (ICFSR): Screening, Diagnosis and Management. The journal of nutrition, health & aging. 2018;22(10):1148-61.
103. Miller DK, Malmstrom TK, Andresen EM, Miller JP, Herning MM, Schootman M, et al. Development and validation of a short portable sarcopenia measure in the African American health project. J Gerontol A Biol Sci Med Sci. 2009;64(3):388-94.
104. Ishii S, Tanaka T, Shibasaki K, Ouchi Y, Kikutani T, Higashiguchi T, et al. Development of a simple screening test for sarcopenia in older adults. Geriatrics & gerontology international. 2014;14 Suppl 1:93-101.
105. Tang T, Wu L, Yang L, Jiaojiao J, Hao Q, Dong B, et al. A sarcopenia screening test predicts mortality in hospitalized older adults. Scientific Reports. 2018;8.
106. Morandi A, Onder G, Fodri L, Sanniti A, Schnelle J, Simmons S, et al. The Association Between the Probability of Sarcopenia and Functional Outcomes in Older Patients Undergoing In-Hospital Rehabilitation. J Am Med Dir Assoc. 2015;16(11):951-6.
107. Rossi AP, Micciolo R, Rubele S, Fantin F, Caliari C, Zoico E, et al. Assessing the Risk of Sarcopenia in the Elderly: The Mini Sarcopenia Risk Assessment (MSRA) Questionnaire. The journal of nutrition, health & aging. 2017;21(6):743-9.
108. Yang M, Hu X, Xie L, Zhang L, Zhou J, Lin J, et al. Validation of the Chinese version of the Mini Sarcopenia Risk Assessment questionnaire in community-dwelling older adults. Medicine (Baltimore). 2018;97(37):e12426.
109. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013;14(8):531-2.
110. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle. 2016;7(1):28-36.
111. Miller DK, Wolinsky FD, Malmstrom TK, Andresen EM, Miller JP. Inner city, middle-aged African Americans have excess frank and subclinical disability. J Gerontol A Biol Sci Med Sci. 2005;60(2):207-12.
112. Woo J, Leung J, Morley JE. Validating the SARC-F: a suitable community screening tool for sarcopenia? J Am Med Dir Assoc. 2014;15(9):630-4.
113. Woo J, Yu R, Leung J. A 3-Item SARC-F. J Am Med Dir Assoc. 2018;19(3):223-8.
114. Barbosa-Silva TG, Menezes AM, Bielemann RM, Malmstrom TK, Gonzalez MC. Enhancing SARC-F: Improving Sarcopenia Screening in the Clinical Practice. J Am Med Dir Assoc. 2016;17(12):1136-41.
115. Shafiee G, Ostovar A, Maleki Birjandi S, Nabipour I, Larijani B, Heshmat R. Development of a Simple and Practical Screening Tool for Detection of Sarcopenia in Older People: The Bushehr Elderly Health Program. Front Med (Lausanne). 2021;8:655759-.
116. Yang M, Hu X, Xie L, Zhang L, Zhou J, Lin J, et al. SARC-F for sarcopenia screening in community-dwelling older adults: Are 3 items enough? Medicine. 2018;97(30):e11726.
117. Goodman MJ, Ghate SR, Mavros P, Sen S, Marcus RL, Joy E, et al. Development of a practical screening tool to predict low muscle mass using NHANES 1999-2004. J Cachexia Sarcopenia Muscle. 2013;4(3):187-97.
118. Yu S, Appleton S, Chapman I, Adams R, Wittert G, Visvanathan T, et al. An anthropometric prediction equation for appendicular skeletal muscle mass in combination with a measure of muscle function to screen for sarcopenia in primary and aged care. J Am Med Dir Assoc. 2015;16(1):25-30.

119. Locquet M, Beaudart C, Reginster J-Y, Petermans J, Bruyère O. Comparison of the performance of five screening methods for sarcopenia. Clin Epidemiol. 2017;10:71-82.
120. Voelker SN, Michalopoulos N, Maier AB, Reijnierse EM. Reliability and Concurrent Validity of the SARC-F and Its Modified Versions: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc. 2021;22(9):1864-76.e16.
121. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc. 2020;21(3):300-7.e2.
122. Reiss J, Iglseder B, Alzner R, Mayr-Pirker B, Pirich C, Kässmann H, et al. Consequences of applying the new EWGSOP2 guideline instead of the former EWGSOP guideline for sarcopenia case finding in older patients. Age and Ageing. 2019;48(5):719-24.
123. Yang M, Lu J, Jiang J, Zeng Y, Tang H. Comparison of four sarcopenia screening tools in nursing home residents. Aging clinical and experimental research. 2018.
124. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet (London, England). 2013;381(9868):752-62.
125. Martin FC, Ranhoff AH. Frailty and Sarcopenia. In: Falaschi P, Marsh D, editors. Orthogeriatrics: The Management of Older Patients with Fragility Fractures. Cham (CH): Springer; 2021. p. 53-65.
126. Laur CV, McNicholl T, Valaitis R, Keller HH. Malnutrition or frailty? Overlap and evidence gaps in the diagnosis and treatment of frailty and malnutrition. Applied Physiology, Nutrition, and Metabolism. 2017;42(5):449-58.
127. Prado CM, Bell JJ, Gonzalez MC. Untangling Malnutrition, Physical Dysfunction, Sarcopenia, Frailty and Cachexia in Ageing. In: Geirsdóttir ÓG, Bell JJ, editors. Interdisciplinary Nutritional Management and Care for Older Adults: An Evidence-Based Practical Guide for Nurses. Cham: Springer International Publishing; 2021. p. 99-113.
128. Puts MTE, Hardt J, Monette J, Girre V, Springall E, Alibhai SMH. Use of geriatric assessment for older adults in the oncology setting: a systematic review. Journal of the National Cancer Institute. 2012;104(15):1133-63.
129. MedlinePlus. Malnutrition. Online: US National Library of Medicine; 2019 [cited 2019 12th September]. Available from: https://medlineplus.gov/ency/article/000404.htm
130. NHS. Overview Malnutrition Online: Crown 2017 [cited 2019 12th September]. Available from: https://www.nhs.uk/conditions/malnutrition/#
131. Merriam-Webster. Malnutrition Online: Merriam-Webster; 2019 [cited 2019 12th September]. Available from: https://www.merriam-webster.com/dictionary/malnutrition.
132. WHO. Malnutrition Online: World Health Organisation; 2019 [cited 2019 12th September]. Available from: https://www.who.int/news-room/fact-sheets/detail/malnutrition
133. Sobotka L. Basics in clinical nutrition. 4 ed: Galen; 2012.
134. BAPEN. Introduction to Malnutrition Online: British Association for Parenteral and Enteral Nutrition; 2019 [cited 2019 12th September 2019]. Available from: https://www.bapen.org.uk/malnutrition-undernutrition/introduction-to-malnutrition
135. Elia M, Ljungqvist, O., Stratton, R.J., Lanham-New, S.A. Clinical Nutrition. 2nd ed: Wiley-Blackwell; 2012.
136. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clinical nutrition (Edinburgh, Scotland). 2017;36(1):49-64.
137. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. JPEN J Parenter Enteral Nutr. 2010;34(2):156-9.

138. National Institute for Health and Clinical Excellence (2006) Nutrition Support for Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition (NICE Guideline CG32), National Collaborating Centre for Acute Care (UK) [
139. Hand RK, Murphy WJ, Field LB, Lee JA, Parrott JS, Ferguson M, et al. Validation of the Academy/ASPEN Malnutrition Clinical Characteristics. Journal of the Academy of Nutrition and Dietetics. 2016;116(5):856-64.
140. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015;34(3):335-40.
141. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewell J, et al. Nutritional assessment: a comparison of clinical judgement and objective measurements. The New England journal of medicine. 1982;306(16):969-72.
142. Guerra RS, Fonseca I, Sousa AS, Jesus A, Pichel F, Amaral TF. ESPEN diagnostic criteria for malnutrition - A validation study in hospitalized patients. Clin Nutr. 2017;36(5):1326-32.
143. Cooper BA, Bartlett LH, Aslani A, Allen BJ, Ibels LS, Pollock CA. Validity of subjective global assessment as a nutritional marker in end-stage renal disease. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2002;40(1):126-32.
144. Sanchez-Rodriguez D, Annweiler C, Ronquillo-Moreno N, Vazquez-Ibar O, Escalada F, Duran X, et al. Prognostic Value of the ESPEN Consensus and Guidelines for Malnutrition: Prediction of Post-Discharge Clinical Outcomes in Older Inpatients. Nutrition in Clinical Practice. 2019;34(2):304-12.
145. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clin Nutr. 2019;38(1):1-9.
146. Ijmker-Hemink V, Heerschop S, Wanten G, van den Berg M. Evaluation of the Validity and Feasibility of the GLIM Criteria Compared with PG-SGA to Diagnose Malnutrition in Relation to One-Year Mortality in Hospitalized Patients. Journal of the Academy of Nutrition and Dietetics. 2021.
147. Theilla M, Rattanachaiwong S, Kagan I, Rigler M, Bendavid I, Singer P. Validation of GLIM malnutrition criteria for diagnosis of malnutrition in ICU patients: An observational study. Clinical Nutrition. 2021;40(5):3578-84.
148. Allard JP, Keller H, Gramlich L, Jeejeebhoy KN, Laporte M, Duerksen DR. GLIM criteria has fair sensitivity and specificity for diagnosing malnutrition when using SGA as comparator. Clin Nutr. 2020;39(9):2771-7.
149. Zhang Z, Wan Z, Zhu Y, Zhang L, Zhang L, Wan H. Prevalence of malnutrition comparing NRS2002, MUST, and PG-SGA with the GLIM criteria in adults with cancer: A multi-center study. Nutrition. 2021;83:111072.
150. White JV, Guenter P, Jensen G, Malone A, Schofield M, Academy of N, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). J Acad Nutr Diet. 2012;112(5):730-8.
151. Nicolini A, Ferrari P, Masoni MC, Fini M, Pagani S, Giampietro O, et al. Malnutrition, anorexia and cachexia in cancer patients: A mini-review on pathogenesis and treatment. Biomedicine & Pharmacotherapy. 2013;67(8):807-17.
152. Chasen MR, Bhargava R. A descriptive review of the factors contributing to nutritional compromise in patients with head and neck cancer. Supportive Care in Cancer. 2009;17(11):1345-51.
153. Alberda C, Graf A, McCargar L. Malnutrition: etiology, consequences, and assessment of a patient at risk. Best practice & research Clinical gastroenterology. 2006;20(3):419-39.
154. Tuca A, Guell E, Martinez-Losada E, Codorniu N. Malignant bowel obstruction in advanced cancer patients: epidemiology, management, and factors influencing spontaneous resolution. Cancer Manag Res. 2012;4:159-69.

155. Cereda E, Pedrolli C, Klersy C, Bonardi C, Quarleri L, Cappello S, et al. Nutritional status in older persons according to healthcare setting: A systematic review and meta-analysis of prevalence data using MNA(®). Clin Nutr. 2016;35(6):1282-90.
156. Elia M. The cost of malnutrition in England and potential cost savings from nutritional interventions (short version). BAPEN NIHR Southamptom Biomedical Research Centre; 2015.
157. Russell CA, Elia, M. NUTRITION SCREENING SURVEYS IN HOSPITALS IN THE UK, 2007-2011 A report based on the amalgamated data from the four Nutrition Screening Week surveys undertaken by BAPEN in 2007, 2008, 2010 and 2011. BAPEN; 2014.
158. Elia M. Screening for Malnutrition: A Multidisciplinary Responsibility. Development and Use of the Malnutrition Universal Screening Tool ('MUST') for Adults. A Report by the Malnutrition Advisory Group of the British Association for Parenteral and Enteral Nutrition. Redditch: BAPEN; 2003.
159. Ryan AM, Prado CM, Sullivan ES, Power DG, Daly LE. Effects of weight loss and sarcopenia on response to chemotherapy, quality of life, and survival. Nutrition. 2019;67-68:110539.
160. Kaegi-Braun N, Mueller M, Schuetz P, Mueller B, Kutz A. Evaluation of Nutritional Support and In-Hospital Mortality in Patients With Malnutrition. JAMA Network Open. 2021;4(1):e2033433-e.
161. Neyens J, Halfens R, Spreeuwenberg M, Meijers J, Luiking Y, Verlaan G, et al. Malnutrition is associated with an increased risk of falls and impaired activity in elderly patients in Dutch residential long-term care (LTC): a cross-sectional study. Archives of gerontology and geriatrics. 2013;56(1):265-9.
162. Guo JJ, Yang H, Qian H, Huang L, Guo Z, Tang T. The effects of different nutritional measurements on delayed wound healing after hip fracture in the elderly. J Surg Res. 2010;159(1):503-8.
163. Zhang X, Edwards BJ. Malnutrition in Older Adults with Cancer. Curr Oncol Rep. 2019;21(9):80.
164. Norman K, Stobaus N, Smoliner C, Zocher D, Scheufele R, Valentini L, et al. Determinants of hand grip strength, knee extension strength and functional status in cancer patients. Clinical nutrition (Edinburgh, Scotland). 2010;29(5):586-91.
165. Barret M, Malka D, Aparicio T, Dalban C, Locher C, Sabate J-M, et al. Nutritional status affects treatment tolerability and survival in metastatic colorectal cancer patients: results of an AGEO prospective multicenter study. Oncology. 2011;81(5-6):395-402.
166. Rasheed S, Woods RT. Malnutrition and quality of life in older people: a systematic review and meta-analysis. Ageing Res Rev. 2013;12(2):561-6.
167. Polanski J, Jankowska-Polanska B, Uchmanowicz I, Chabowski M, Janczak D, Mazur G, et al. Malnutrition and Quality of Life in Patients with Non-Small-Cell Lung Cancer. Advances in experimental medicine and biology. 2017;1021:15-26.
168. Decoster L, Quinten C, Kenis C, Flamaing J, Debruyne PR, De Groof I, et al. Health related quality of life in older patients with solid tumors and prognostic factors for decline. J Geriatr Oncol. 2019.
169. Langius JA, Zandbergen MC, Eerenstein SE, van Tulder MW, Leemans CR, Kramer MH, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. Clin Nutr. 2013;32(5):671-8.
170. Layer P, Kashirskaya N, Gubergrits N. Contribution of pancreatic enzyme replacement therapy to survival and quality of life in patients with pancreatic exocrine insufficiency. World J Gastroenterol. 2019;25(20):2430-41.
171. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11-48.
172. BDA. Manual of Dietetic Practice. 6th ed. Oxford: Wiley Blackwell; 2019.

173. NICE. Boarderline substances online 2019 [cited 2019 04 October]. Available from: https://bnf.nice.org.uk/borderline-substance-taxonomy/
174. NICE. Cancer of the upper aerodigestive tract: assessment and management in people aed 16 and over. online: NICE; 2016.
175. Druml C, Ballmer PE, Druml W, Oehmichen F, Shenkin A, Singer P, et al. ESPEN guideline on ethical aspects of artificial nutrition and hydration. Clin Nutr. 2016;35(3):545-56.
176. Tobberup R, Thoresen L, Falkmer UG, Yilmaz MK, Solheim TS, Balstad TR. Effects of current parenteral nutrition treatment on health-related quality of life, physical function, nutritional status, survival and adverse events exclusively in patients with advanced cancer: A systematic literature review. Crit Rev Oncol Hematol. 2019;139:96-107.
177. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. The journal of nutrition, health & aging. 2009;13(9):782-8.
178. Lim SL, Tong CY, Ang E, Lee EJ, Loke WC, Chen Y, et al. Development and validation of 3-Minute Nutrition Screening (3-MinNS) tool for acute hospital patients in Singapore. Asia Pacific journal of clinical nutrition. 2009;18(3):395-403.
179. Tah PC, Kee CC, Majid HA. Validity and Reliability of a Nutrition Screening Tool in Identifying Malnutrition Among Hospitalized Adult Patients. Nutr Clin Pract. 2019.
180. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321-36.
181. Phillips MB, Foley AL, Barnard R, Isenring EA, Miller MD. Nutritional screening in community-dwelling older adults: a systematic literature review. Asia Pac J Clin Nutr. 2010;19(3):440-9.
182. Wong S, Derry F, Jamous A, Hirani SP, Grimble G, Forbes A. Validation of the spinal nutrition screening tool (SNST) in patients with spinal cord injuries (SCI): result from a multicentre study. European Journal of Clinical Nutrition. 2012;66(3):382-7.
183. Jensen GL, Bistrian B, Roubenoff R, Heimburger DC. Malnutrition syndromes: a conundrum vs continuum. JPEN Journal of parenteral and enteral nutrition. 2009;33(6):710-6.
184. Feinberg J, Nielsen EE, Korang SK, Halberg Engell K, Nielsen MS, Zhang K, et al. Nutrition support in hospitalised adults at nutritional risk. The Cochrane database of systematic reviews. 2017;5:Cd011598.
185. Woolf SH, Harris R. The Harms of Screening: New Attention to an Old Concern. JAMA. 2012;307(6):565-6.
186. Kuhn TS. The structure of scientific revolutions. University of Chicago Press: Chicago; 1962.
187. Guba EG. The paradigm dialog. Guba EG, editor. Thousand Oaks, CA, US: Sage Publications, Inc; 1990. 424- p.
188. Crotty M. The Foundations of Social Research: Meaning and Perspective in the Research Process. Crotty M, editor. London: SAGE publications Inc. ; 1998.
189. Al-Saadi H. Demystifying Ontology and Epistemology in Research Methods. 2014.
190. Snape D, Spencer, L. The foundations of qualitative research In J. Richie & J. Lewis (Eds.) Qualitative Research Practices. Los Angeles: Sage; 2003.
191. Bryman A. Social Research Methods. 4 ed. Oxford: Oxford Univeristy Press; 2001.
192. Palinkas LA, Mendon SJ, Hamilton AB. Innovations in Mixed Methods Evaluations. Annu Rev Public Health. 2019;40:423-42.
193. Brannen J. Mixed Methods Research: A Discussion Paper. ESRC National Centre for Research Methods, Methods Review Paper (NCRM). 2005.
194. Tashakkori A, Teddlie, C. Mixed Methodology: Combining Qualitative and Quantitative Approaches. Thousand Oaks: SAGE Publications; 1998.
195. Feilzer M, Y. Doing Mixed Methods Research Pragmatically: Implications for the Rediscovery of Pragmatism as a Research Paradigm. Journal of Mixed Methods Research. 2009;4(1):6-16.
196. Bryman A. The Research Question in Social Research: What is its Role? International Journal of Social Research Methodology. 2007;10(1):5-20.

197. Glogowska M. Paradigms, pragmatism and possibilities: mixed-methods research in speech and language therapy. Int J Lang Commun Disord. 2011;46(3):251-60.
198. The SAGE Handbook of Qualitative Methods in Health Research. 2010 2021/05/05. London: SAGE Publications Ltd. Available from: https://methods.sagepub.com/book/sage-hdbk-qualitative-methods-in-health-research.
199. Ida S, Murata K, Nakadachi D, Ishihara Y, Imataka K, Uchida A, et al. Development of a Japanese version of the SARC-F for diabetic patients: an examination of reliability and validity. Aging clinical and experimental research. 2017;29(5):935-42.
200. Kera T, Kawai H, Hirano H, Kojima M, Watanabe Y, Motokawa K, et al. SARC-F: A validation study with community-dwelling older Japanese adults. Geriatrics & gerontology international. 2019.
201. Lesko L, Zineh I, Huang SM. What Is Clinical Utility and Why Should We Care? Clinical pharmacology and therapeutics. 2010;88:729-33.
202. Cancer Research UK. Cancer Incidence Statistics Online: Cancer Research UK; 2019 [Available from: www.cancerresearchuk.org/health-professional/cancer-statistics/incidence.
203. Kingston A, Comas-Herrera A, Jagger C. Forecasting the care needs of the older population in England over the next 20 years: estimates from the Population Ageing and Care Simulation (PACSim) modelling study. Lancet Public Health. 2018;3(9):e447-e55.
204. de Morais C, Oliveira B, Afonso C, Lumbers M, Raats M, de Almeida MD. Nutritional risk of European elderly. Eur J Clin Nutr. 2013;67(11):1215-9.
205. Nicolini A, Ferrari P, Masoni MC, Fini M, Pagani S, Giampietro O, et al. Malnutrition, anorexia and cachexia in cancer patients: A mini-review on pathogenesis and treatment. Biomed Pharmacother. 2013;67(8):807-17.
206. Anker MS, Holcomb R, Muscaritoli M, von Haehling S, Haverkamp W, Jatoi A, et al. Orphan disease status of cancer cachexia in the USA and in the European Union: a systematic review. J Cachexia Sarcopenia Muscle. 2019;10(1):22-34.
207. Wisdom M, Creswell, J.W. Integrating Quantitative and Qualitative Data Collection and Analysis While Studying Patient-Centered Medical Home Models. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
208. Green J, Caracelli, V.J., Graham, W.F. Towards a conceptual framework for mixed-method evaluation designs. Education, Evaluation and Policy Analysis. 1989;11(3):255-74.
209. Lind J. A treatise of the scurvy. In three parts. Containing an inquiry into the nature, causes, and cure, of that disease. Together with a critical and chronological view of what has been published on the subject. Edinburgh: Sands, Murray and Cochran for A. Kincaid & A. Donaldson; 1753.
210. Hughes RE. James Lind and the cure of scurvy: an experimental approach. Medical History. 1975;19:342-51.
211. Sutton A, Clowes M, Preston L, Booth A. Meeting the review family: exploring review types and associated information retrieval requirements. Health Information & Libraries Journal. 2019;36(3):202-22.
212. Jahan N, Naveed S, Zeshan M, Tahir MA. How to Conduct a Systematic Review: A Narrative Literature Review. Cureus. 2016;8(11):e864-e.
213. Robinson P, Lowe J. Literature reviews vs systematic reviews. Australian and New Zealand Journal of Public Health. 2015;39.
214. Pham MT, Rajić A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. Res Synth Methods. 2014;5(4):371-85.
215. Baird R. Systematic reviews and meta-analytic techniques. Seminars in Pediatric Surgery. 2018;27(6):338-44.
216. Baker KA, Weeks SM. An Overview of Systematic Review. Journal of PeriAnesthesia Nursing. 2014;29(6):454-8.

217. Mallett R, Hagen-Zanker J, Slater R, Duvendack M. The benefits and challenges of using systematic reviews in international development research. Journal of Development Effectiveness. 2012;4(3):445-55.
218. Bown MJ, Sutton AJ. Quality Control in Systematic Reviews and Meta-analyses. European Journal of Vascular and Endovascular Surgery. 2010;40(5):669-77.
219. Gopalakrishnan S, Ganeshkumar P. Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. J Family Med Prim Care. 2013;2(1):9-14.
220. NIHR. PROSPERO International prospective register of systematic reviews [online]: National Institute for Health Research; 2019 [cited 2019 14th November]. Available from: https://www.crd.york.ac.uk/prospero/#aboutpage.
221. Bullock A, McKenzie, G., Greenley, S., Paton, L., Johnson, M. . Systematic review of the literature investigating the validity of proxy measures of malnutrition in the older cancer patient CRD420191209912019 [updated 17th June 201917th July 2019]. Available from: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=120991.
222. Kluwer W. Ovid MEDLINE [online]: Wolters Kluwer; 2019 [cited 2019 14th November]. Available from: https://www.ovid.com/product-details.901.html.
223. Elsevier. Embase [online] Elsevier; 2019 [cited 2019 14th November]. Available from: https://www.elsevier.com/en-gb/solutions/embase-biomedical-research.
224. Analytics C. Web of Science [online]: Clarivate Analytics; 2019 [cited 2019 14th November]. Available from: https://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch&SID=E1WCSmsRSBx7vXmD8EQ&preferencesSaved=.
225. Industries E. CINAHL COMPLETE [online] EBSCO Nursing Resources; 2019 [cited 2019 14th November]. Available from: https://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete.
226. ProQuest. British Nursing Database [online]: ProQuest; 2019 [cited 2019 14th November]. Available from: https://www.proquest.com/products-services/bnd.html.
227. WILEY. Cochrane Library [online]: WILEY; 2019 [cited 2019 14th November]. Available from: https://www.cochranelibrary.com.
228. PsycINFO. PsycINFO [online]: American Psychological Association; 2019 [cited 2019 13th December]. Available from: https://www.apa.org/pubs/databases/psycinfo/
229. Lemeshow AR, Blum RE, Berlin JA, Stoto MA, Colditz GA. Searching one or two databases was insufficient for meta-analysis of observational studies. Journal of clinical epidemiology. 2005;58(9):867-73.
230. Lorenzetti DL, Topfer LA, Dennett L, Clement F. Value of databases other than medline for rapid health technology assessments. International journal of technology assessment in health care. 2014;30(2):173-8.
231. Golder S, Loke YK. The contribution of different information sources for adverse effects data. International journal of technology assessment in health care. 2012;28(2):133-7.
232. Hinde S, Spackman E. Bidirectional citation searching to completion: an exploration of literature searching methods. PharmacoEconomics. 2015;33(1):5-11.
233. Beyer FR, Wright K. Can we prioritise which databases to search? A case study using a systematic review of frozen shoulder management. Health information and libraries journal. 2013;30(1):49-58.
234. Chapman AL, Morgan LC, Gartlehner G. Semi-automating the manual literature search for systematic reviews increases efficiency. Health information and libraries journal. 2010;27(1):22-7.
235. Linder SK, Kamath GR, Pratt GF, Saraykar SS, Volk RJ. Citation searches are more sensitive than keyword searches to identify studies using specific measurement instruments. Journal of clinical epidemiology. 2015;68(4):412-7.

236. Hausner E, Waffenschmidt, S. Value of using different seach approaches [online]: HTA Vortal; 2019 [cited 2019 14th November]. Available from: http://vortal.htai.org/index.php?q=node/993.
237. CASP Cohort Study Checklist [online] Critical Appraisal Skills Programme; 2018 [cited 2019 07 December]. Available from: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Cohort-Study-Checklist-2018_fillable_form.pdf.
238. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ open. 2016;6(12):e011458-e.
239. Wells GA, Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M. Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [online]2019 [Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4877518/#b10-epih-38-e2016014.
240. Pluye P, Hong QN. Combining the Power of Stories and the Power of Numbers: Mixed Methods Research and Mixed Studies Reviews. Annual Review of Public Health. 2014;35(1):29-45.
241. Haidich AB. Meta-analysis in medical research. Hippokratia. 2010;14(Suppl 1):29-37.
242. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011;342:d549.
243. Melsen WG, Bootsma MCJ, Rovers MM, Bonten MJM. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clinical Microbiology and Infection. 2014;20(2):123-9.
244. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC medical research methodology. 2015;15:35-.
245. CRD. Systematic Reviews: CRD's guidance for undetaking reviews in health care. York: Centre for Reviews and Dissemination; 2008.
246. Pawson R, Greenhalgh T, Harvey G, Walshe K. Realist review - a new method of systematic review designed for complex policy interventions. Journal of Health Services Research & Policy. 2005;10(1_suppl):21-34.
247. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Medical Research Methodology. 2013;13(1):117.
248. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Medical Research Methodology. 2008;8(1):45.
249. Nowell LS, Norris JM, White DE, Moules NJ. Thematic Analysis:Striving to Meet the Trustworthiness Criteria. International Journal of Qualitative Methods. 2017;16(1):1609406917733847.
250. Weaver CM, Miller JW. Challenges in conducting clinical nutrition research. Nutr Rev. 2017;75(7):491-9.
251. Thiese MS. Observational and interventional study design types; an overview. Biochem Med (Zagreb). 2014;24(2):199-210.
252. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emergency Medicine Journal. 2003;20(1):54-60.
253. Wade A. Derivation versus validation. Arch Dis Child. 2000;83(6):459-60.
254. Smith PG, Morrow, R.H., Ross, D.A. Field Trials of Health Interventions: A Toolbox. 3rd Ed. ed. Oxford: OUP Oxford; 2015.
255. Wang X, Cheng Z. Cross-Sectional Studies: Strengths, Weaknesses, and Recommendations. Chest. 2020;158(1s):S65-s71.
256. Setia MS. Methodology Series Module 3: Cross-sectional Studies. Indian journal of dermatology. 2016;61(3):261-4.
257. Song JW, Chung KC. Observational studies: cohort and case-control studies. Plast Reconstr Surg. 2010;126(6):2234-42.

258. Benjamin RS. Observational studies: goldmines of information on rare diseases. BMC Med. 2017;15(1):100-.
259. Setia MS. Methodology Series Module 5: Sampling Strategies. Indian journal of dermatology. 2016;61(5):505-9.
260. Starks H, Diehr P, Curtis JR. The challenge of selection bias and confounding in palliative care research. J Palliat Med. 2009;12(2):181-7.
261. Gysels MH, Evans C, Higginson IJ. Patient, caregiver, health professional and researcher views and experiences of participating in research at the end of life: a critical interpretive synthesis of the literature. BMC Med Res Methodol. 2012;12:123.
262. Preston N, Payne S, Salt S, Griggs A, Rigby J, Parr A, et al. ARE PALLIATIVE CARE RESEARCH SAMPLES BIASED? RESULTS FROM INTERVIEWS WITH EXPERIENCED PALLIATIVE CARE STAFF. BMJ Supportive & Palliative Care. 2013;3(1):130-.
263. Oliver A, Greenberg CC. Measuring outcomes in oncology treatment: the importance of patient-centered outcomes. Surg Clin North Am. 2009;89(1):17-25, vii.
264. Iwashyna TJ, McPeake J. Choosing outcomes for clinical trials: a pragmatic perspective. Curr Opin Crit Care. 2018;24(5):428-33.
265. Cong M, Song C, Xu H, Song C, Wang C, Fu Z, et al. The patient-generated subjective global assessment is a promising screening tool for cancer cachexia. BMJ Support Palliat Care. 2020.
266. Souza NC, Gonzalez MC, Martucci RB, Rodrigues VD, de Pinho NB, Qureshi AR, et al. Comparative Analysis Between Computed Tomography and Surrogate Methods to Detect Low Muscle Mass Among Colorectal Cancer Patients. JPEN Journal of parenteral and enteral nutrition. 2019.
267. Nwosu AC, Mayland CR, Mason S, Cox TF, Varro A, Stanley S, et al. Bioelectrical impedance vector analysis (BIVA) as a method to compare body composition differences according to cancer stage and type. Clinical Nutrition ESPEN. 2019;30:59-66.
268. Walowski CO, Braun W, Maisch MJ, Jensen B, Peine S, Norman K, et al. Reference Values for Skeletal Muscle Mass - Current Concepts and Methodological Considerations. Nutrients. 2020;12(3):755.
269. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8):755-63.
270. Skeie E, Tangvik RJ, Nymo LS, Harthug S, Lassen K, Viste A. Weight loss and BMI criteria in GLIM's definition of malnutrition is associated with postoperative complications following abdominal resections - Results from a National Quality Registry. Clin Nutr. 2020;39(5):1593-9.
271. Hickson M. Malnutrition and ageing. Postgrad Med J. 2006;82(963):2-8.
272. Gibson RS. Principles of Nutritional Assessment. 1st Ed. ed. New York: Oxford University Press; 2005.
273. Cattermole GN, Graham CA, Rainer TH. Mid-arm circumference can be used to estimate weight of adult and adolescent patients. Emerg Med J. 2017;34(4):231-6.
274. Wu L-W, Lin Y-Y, Kao T-W, Lin C-M, Wang C-C, Wang G-C, et al. Mid-Arm Circumference and All-Cause, Cardiovascular, and Cancer Mortality among Obese and Non-Obese US Adults: the National Health and Nutrition Examination Survey III. Scientific reports. 2017;7(1):2302-.
275. Flood A, Chung A, Parker H, Kearns V, O'Sullivan TA. The use of hand grip strength as a predictor of nutrition status in hospital patients. Clin Nutr. 2014;33(1):106-14.
276. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing. 2011;40(4):423-9.
277. Sousa-Santos AR, Amaral TF. Differences in handgrip strength protocols to identify sarcopenia and frailty - a systematic review. BMC Geriatr. 2017;17(1):238.
278. Contreras-Bolívar V, Sánchez-Torralvo FJ, Ruiz-Vico M, González-Almendros I, Barrios M, Padín S, et al. GLIM Criteria Using Hand Grip Strength Adequately Predict Six-Month Mortality in Cancer Inpatients. Nutrients. 2019;11(9).

279. Celis-Morales CA, Welsh P, Lyall DM, Steell L, Petermann F, Anderson J, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. BMJ. 2018;361:k1651.
280. Hull HR, Thornton J, Wang J, Pierson RN, Jr., Kaleem Z, Pi-Sunyer X, et al. Fat-free mass index: changes and race/ethnic differences in adulthood. Int J Obes (Lond). 2011;35(1):121-7.
281. Kyle UG, Schutz Y, Dupertuis YM, Pichard C. Body composition interpretation. Contributions of the fat-free mass index and the body fat mass index. Nutrition. 2003;19(7-8):597-604.
282. Shafiee G, Ostovar A, Heshmat R, Keshtkar A, Sharifi F, Shadman Z, et al. Appendicular Skeletal Muscle Mass Reference Values and the Peak Muscle Mass to Identify Sarcopenia among Iranian Healthy Population. International Journal of Preventive Medicine. 2018;9(1):25.
283. Beaudart C, McCloskey E, Bruyère O, Cesari M, Rolland Y, Rizzoli R, et al. Sarcopenia in daily practice: assessment and management. BMC Geriatr. 2016;16(1):170.
284. Cesari M, Kritchevsky SB, Newman AB, Simonsick EM, Harris TB, Penninx BW, et al. Added value of physical performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. Journal of the American Geriatrics Society. 2009;57(2):251-9.
285. Lord SR, Murray SM, Chapman K, Munro B, Tiedemann A. Sit-to-stand performance depends on sensation, speed, balance, and psychological status in addition to strength in older people. The journals of gerontology Series A, Biological sciences and medical sciences. 2002;57(8):M539-43.
286. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. Journal of the American Geriatrics Society. 1991;39(2):142-8.
287. Lyders Johansen K, Derby Stistrup R, Skibdal Schjøtt C, Madsen J, Vinther A. Absolute and Relative Reliability of the Timed 'Up & Go' Test and '30second Chair-Stand' Test in Hospitalised Patients with Stroke. PLoS One. 2016;11(10):e0165663.
288. Cooper H, Camic, P., Long, D.L., Panter, A.T., Rindskopf, D., Sher, K. APA handbook of research methods in psychology, Vol 2: Research designs: Quantitative, qualitative, neuropsychological, and biological. Cooper H, Camic PM, Long DL, Panter AT, Rindskopf D, Sher KJ, editors. Washington, DC, US: American Psychological Association; 2012. x, 701-x, p.
289. The SAGE Encyclopedia of Qualitative Research Methods. Given LM, editor. Thousand Oaks, California2008 2019/11/04.
290. Galdas P. Revisiting Bias in Qualitative Research:Reflections on Its Relationship With Funding and Impact. International Journal of Qualitative Methods. 2017;16(1):1609406917748992.
291. Barrett D, Twycross A. Data collection in qualitative research. Evidence Based Nursing. 2018;21(3):63-4.
292. Chun Tie Y, Birks M, Francis K. Grounded theory research: A design framework for novice researchers. SAGE Open Med. 2019;7:2050312118822927-.
293. Rodriguez A, Smith J. Phenomenology as a healthcare research method. Evidence Based Nursing. 2018;21(4):96-8.
294. Neubauer BE, Witkop CT, Varpio L. How phenomenology can help us learn from the experiences of others. Perspectives on Medical Education. 2019;8(2):90-7.
295. Noble H, Smith J. Issues of validity and reliability in qualitative research. Evidence Based Nursing. 2015;18(2):34-5.
296. APA handbook of research methods in psychology, Vol 2: Research designs: Quantitative, qualitative, neuropsychological, and biological. Cooper H, Camic PM, Long DL, Panter AT, Rindskopf D, Sher KJ, editors. Washington, DC, US: American Psychological Association; 2012. x, 701-x, p.
297. Jamshed S. Qualitative research method-interviewing and observation. J Basic Clin Pharm. 2014;5(4):87-8.
298. Corbin J, Morse JM. The Unstructured Interactive Interview: Issues of Reciprocity and Risks when Dealing with Sensitive Topics. Qualitative Inquiry. 2003;9(3):335-54.
299. Halcomb EJ, Davidson PM. Is verbatim transcription of interview data always necessary? Applied Nursing Research. 2006;19(1):38-42.

300. Braun V, Clarke V. To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample-size rationales. Qualitative Research in Sport, Exercise and Health. 2021;13(2):201-16.
301. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res. 2016;26(13):1753-60.
302. Low J. A Pragmatic Definition of the Concept of Theoretical Saturation. Sociological Focus. 2019;52(2):131-9.
303. Smith B. Generalizability in qualitative research: misunderstandings, opportunities and recommendations for the sport and exercise sciences. Qualitative Research in Sport, Exercise and Health. 2018;10(1):137-49.
304. Tomaszewski LE, Zarestky J, Gonzalez E. Planning Qualitative Research: Design and Decision Making for New Researchers. International Journal of Qualitative Methods. 2020;19:1609406920967174.
305. Smith JA, Shinebourne P. Interpretative phenomenological analysis: American Psychological Association; 2012.
306. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77-101.
307. Sundler AJ, Lindberg E, Nilsson C, Palmér L. Qualitative thematic analysis based on descriptive phenomenology. Nurs Open. 2019;6(3):733-9.
308. Applied Thematic Analysis. 2012 2021/06/15. Thousand Oaks, California: SAGE Publications, Inc. Available from: https://methods.sagepub.com/book/applied-thematic-analysis.
309. Dapkus MA. A thematic analysis of the experience of time. J Pers Soc Psychol. 1985;49(2):408-19.
310. Lize N, V IJ-H, van Lieshout R, Wijnholds-Roeters Y, van den Berg M, Soud MY, et al. Experiences of patients with cancer with information and support for psychosocial consequences of reduced ability to eat: a qualitative interview study. Support Care Cancer. 2021.
311. Halkett GK, Golding RM, Langbecker D, White R, Jackson M, Kernutt E, et al. From the carer's mouth: A phenomenological exploration of carer experiences with head and neck cancer patients. Psychooncology. 2020;29(10):1695-703.
312. Braun V, Clarke V. What can "thematic analysis" offer health and wellbeing researchers? Int J Qual Stud Health Well-being. 2014;9:26152-.
313. Richmond B. Systems Thinking/System Dynamics: Let's Just Get on with It. System Dynamics Review. 2006;10:135-57.
314. Baugh Littlejohns L, Baum F, Lawless A, Freeman T. The value of a causal loop diagram in exploring the complex interplay of factors that influence health promotion in a multisectoral health system in Australia. Health Research Policy and Systems. 2018;16(1):126.
315. Martin CM, Sturmberg JP. Perturbing ongoing conversations about systems and complexity in health services and systems. J Eval Clin Pract. 2009;15(3):549-52.
316. Sterman JD. Business Dynamics: System Thinking and Modeling for a Complex World. Boston, MA, USA: Irwin McGraw-Hill; 2001.
317. Chen H, Walabyeki J, Johnson M, Boland E, Seymour J, Macleod U. An integrated understanding of the complex drivers of emergency presentations and admissions in cancer patients: Qualitative modelling of secondary-care health professionals' experiences and views. PLoS One. 2019;14(5):e0216430.
318. Owen B, Brown AD, Kuhlberg J, Millar L, Nichols M, Economos C, et al. Understanding a successful obesity prevention initiative in children under 5 from a systems perspective. PloS one. 2018;13(3):e0195141-e.
319. Peters DH. The application of systems thinking in health: why use systems thinking? Health Research Policy and Systems. 2014;12(1):51.
320. Heyvaert M, Hannes K, Maes B, Onghena P. Critical Appraisal of Mixed Methods Studies. Journal of Mixed Methods Research. 2013;7(4):302-27.

321. Dellinger AB, Leech NL. Toward a Unified Validation Framework in Mixed Methods Research. Journal of Mixed Methods Research. 2007;1(4):309-32.
322. Johnson RE, Grove AL, Clarke A. Pillar Integration Process: A Joint Display Technique to Integrate Data in Mixed Methods Research. Journal of Mixed Methods Research. 2019;13(3):301-20.
323. Stern C, Lizarondo L, Carrier J, Godfrey C, Rieger K, Salmond S, et al. Methodological guidance for the conduct of mixed methods systematic reviews. JBI Evid Synth. 2020;18(10):2108-18.
324. Dixon-Woods M, Cavers D, Agarwal S, Annandale E, Arthur A, Harvey J, et al. Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups. BMC Medical Research Methodology. 2006;6(1):35.
325. Dixon-Woods M. Critical interpretive synthesis: what it is and why it is needed. In: Come to the craic. Abstracts of the 14th Cochrane Colloquium; 2006 23-26 Oct; Dublin, UK. 2006.
326. Depraetere J, Vandeviver C, Keygnaert I, Beken TV. The critical interpretive synthesis: an assessment of reporting practices. International Journal of Social Research Methodology. 2020:1-21.
327. Dixon-Woods M. Critical interpretive synthesis: what it is and why it is needed. In. Come to the craic. Abstracts of the 14th Cochrane Colloquium, Dublin, UK. 2006.
328. Flemming K. Synthesis of quantitative and qualitative research: an example using Critical Interpretive Synthesis. Journal of advanced nursing. 2010;66 1:201-17.
329. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. Journal of Clinical Oncology. 2018;36(22):2326-47.
330. Huisman MG, Kok M, de Bock GH, van Leeuwen BL. Delivering tailored surgery to older cancer patients: Preoperative geriatric assessment domains and screening tools - A systematic review of systematic reviews. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2017;43(1):1-14.
331. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi. 1984;85(9):1001-5.
332. Duerksen DR, Yeo TA, Siemens JL, O'Connor MP. The validity and reproducibility of clinical assessment of nutritional status in the elderly. Nutrition (Burbank, Los Angeles County, Calif). 2000;16(9):740-4.
333. da Silva Fink J, Daniel de Mello P, Daniel de Mello E. Subjective global assessment of nutritional status - A systematic review of the literature. Clinical nutrition (Edinburgh, Scotland). 2015;34(5):785-92.
334. Ozkalkanli MY, Ozkalkanli DT, Katircioglu K, Savaci S. Comparison of tools for nutrition assessment and screening for predicting the development of complications in orthopedic surgery. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2009;24(2):274-80.
335. Raslan M, Gonzalez MC, Torrinhas RS, Ravacci GR, Pereira JC, Waitzberg DL. Complementarity of Subjective Global Assessment (SGA) and Nutritional Risk Screening 2002 (NRS 2002) for predicting poor clinical outcomes in hospitalized patients. Clinical nutrition (Edinburgh, Scotland). 2011;30(1):49-53.
336. Weekes CE, Elia M, Emery PW. The development, validation and reliability of a nutrition screening tool based on the recommendations of the British Association for Parenteral and Enteral Nutrition (BAPEN). Clinical nutrition (Edinburgh, Scotland). 2004;23(5):1104-12.
337. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren MA. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ). Clinical nutrition (Edinburgh, Scotland). 2005;24(1):75-82.
338. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
339. Hu Y, Shen J, Liu R, Feng Z, Zhang C, Ling L, et al. Prognostic value of pretreatment prognostic nutritional index in non-small cell lung cancer: A systematic review and meta-analysis. Int J Biol Markers. 2018;33(4):372-8.

340. Sun K, Chen S, Xu J, Li G, He Y. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2014;140(9):1537-49.
341. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. European journal of cancer (Oxford, England : 1990). 1996;32a(7):1135-41.
342. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc. 2016;104(3):240-3.
343. Wallace B, Small K, Brodley C, Lau J, Trikalinos T. Deploying an interactive machine learning system in an Evidence-based Practice Center: Abstrackr. Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium. 2012;819.
344. Review Manager (RevMan) [Computer Program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration 2014.
345. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557-60.
346. Aaldriks AA, Giltay EJ, le Cessie S, van der Geest LG, Portielje JE, Tanis BC, et al. Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy. Breast. 2013;22(5):753-60.
347. Aaldriks AA, Giltay EJ, Nortier JW, van der Geest LG, Tanis BC, Ypma P, et al. Prognostic significance of geriatric assessment in combination with laboratory parameters in elderly patients with aggressive non-Hodgkin lymphoma. Leuk Lymphoma. 2015;56(4):927-35.
348. Aaldriks AA, Maartense E, Nortier HJ, van der Geest LG, le Cessie S, Tanis BC, et al. Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the elderly. Acta Oncol. 2016;55(1):15-23.
349. Baitar A, Kenis C, Decoster L, De Greve J, Lobelle JP, Flamaing J, et al. The prognostic value of 3 commonly measured blood parameters and geriatric assessment to predict overall survival in addition to clinical information in older patients with cancer. Cancer. 2018;124(18):3764-75.
350. Bourdel-Marchasson I, Diallo A, Bellera C, Blanc-Bisson C, Durrieu J, Germain C, et al. One-Year Mortality in Older Patients with Cancer: Development and External Validation of an MNA-Based Prognostic Score. PloS one. 2016;11(2):e0148523.
351. Chaufour-Andre C, Bajard A, Fingal C, Roux P, Fiorletta I, Gertych W, et al. Nutritional impacts of cancer surgery in the elderly. Prospective and descriptive study. Nutrition Clinique et Metabolisme. 2011;25(1):5-13.
352. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012;118(13):3377-86.
353. Hoppe S, Rainfray M, Fonck M, Hoppenreys L, Blanc JF, Ceccaldi J, et al. Functional decline in older patients with cancer receiving first-line chemotherapy. J Clin Oncol. 2013;31(31):3877-82.
354. Hsu T, Chen R, Lin SC, Djalalov S, Horgan A, Le LW, et al. Pilot of three objective markers of physical health and chemotherapy toxicity in older adults. Current oncology (Toronto, Ont). 2015;22(6):385-91.
355. Kaibori M, Ishizaki M, Matsui K, Iida H, Inoue K, Nagashima F, et al. Geriatric assessment as a predictor of postoperative complications in elderly patients with hepatocellular carcinoma. Langenbeck's archives of surgery. 2016;401(2):205-14.
356. Kanesvaran R, Li H, Koo KN, Poon D. Analysis of prognostic factors of comprehensive geriatric assessment and development of a clinical scoring system in elderly Asian patients with cancer. J Clin Oncol. 2011;29(27):3620-7.
357. Kim JW, Lee YG, Hwang IG, Song HS, Koh SJ, Ko YH, et al. Predicting cumulative incidence of adverse events in older patients with cancer undergoing first-line palliative chemotherapy: Korean Cancer Study Group (KCSG) multicentre prospective study. Br J Cancer. 2018;118(9):1169-75.

358. Lu J, Cao LL, Zheng CH, Li P, Xie JW, Wang JB, et al. The Preoperative Frailty Versus Inflammation-Based Prognostic Score: Which is Better as an Objective Predictor for Gastric Cancer Patients 80 Years and Older? Ann Surg Oncol. 2017;24(3):754-62.
359. Marenco D, Marinello R, Berruti A, Gaspari F, Stasi MF, Rosato R, et al. Multidimensional geriatric assessment in treatment decision in elderly cancer patients: 6-year experience in an outpatient geriatric oncology service. Crit Rev Oncol Hematol. 2008;68(2):157-64.
360. Fiorelli A, Vicidomini G, Mazzella A, Messina G, Milione R, Di Crescenzo VG, et al. The influence of body mass index and weight loss on outcome of elderly patients undergoing lung cancer resection. The Thoracic and cardiovascular surgeon. 2014;62(7):578-87.
361. Harimoto N, Yoshizumi T, Shimokawa M, Sakata K, Kimura K, Itoh S, et al. Sarcopenia is a poor prognostic factor following hepatic resection in patients aged 70 years and older with hepatocellular carcinoma. Hepatology research : the official journal of the Japan Society of Hepatology. 2016;46(12):1247-55.
362. Kim SW, Kim MY, Lee YP, Ryu YJ, Lee SJ, Lee JH, et al. Clinical features and prognostic factors in elderly koreans with advanced non-small-cell lung cancer in a tertiary referral hospital. Tuberculosis and respiratory diseases. 2013;75(2):52-8.
363. Kushiyama S, Sakurai K, Kubo N, Tamamori Y, Nishii T, Tachimori A, et al. The Preoperative Geriatric Nutritional Risk Index Predicts Postoperative Complications in Elderly Patients with Gastric Cancer Undergoing Gastrectomy. In vivo (Athens, Greece). 2018;32(6):1667-72.
364. Lai P, Sud S, Zhang T, Asmis T, Wheatley-Price P. Palliative chemotherapy in advanced colorectal cancer patients 80 years of age and older. Current oncology (Toronto, Ont). 2016;23(3):144-53.
365. Mikami K, Hirano K, Futami K, Maekawa T. Gastrectomy with limited surgery for elderly patients with gastric cancer. Asian journal of surgery. 2018;41(1):65-72.
366. Mosk CA, van Vugt JLA, de Jonge H, Witjes CD, Buettner S, Ijzermans JN, et al. Low skeletal muscle mass as a risk factor for postoperative delirium in elderly patients undergoing colorectal cancer surgery. Clin Interv Aging. 2018;13:2097-106.
367. Neuman HB, Weiss JM, Leverson G, O'Connor ES, Greenblatt DY, Loconte NK, et al. Predictors of short-term postoperative survival after elective colectomy in colon cancer patients >/= 80 years of age. Ann Surg Oncol. 2013;20(5):1427-35.
368. Sakurai K, Tamura T, Toyokawa T, Amano R, Kubo N, Tanaka H, et al. Low Preoperative Prognostic Nutritional Index Predicts Poor Survival Post-gastrectomy in Elderly Patients with Gastric Cancer. Annals of surgical oncology. 2016;23(11):3669-76.
369. Sakurai K, Kubo N, Tamamori Y, Tamura T, Toyokawa T, Tanaka H, et al. Long-term survival estimates in older patients with pathological stage I gastric cancer undergoing gastrectomy: Duocentric analysis of simplified scoring system. J Geriatr Oncol. 2019.
370. Sekiguchi M, Oda I, Suzuki H, Abe S, Nonaka S, Yoshinaga S, et al. Clinical outcomes and prognostic factors in gastric cancer patients aged >/=85 years undergoing endoscopic submucosal dissection. Gastrointest Endosc. 2017;85(5):963-72.
371. Shoji F, Miura N, Matsubara T, Akamine T, Kozuma Y, Haratake N, et al. Prognostic significance of immune-nutritional parameters for surgically resected elderly lung cancer patients: a multicentre retrospective study. Interactive cardiovascular and thoracic surgery. 2018;26(3):389-94.
372. Stangl-Kremser J, D'Andrea D, Vartolomei M, Abufaraj M, Goldner G, Baltzer P, et al. Prognostic value of nutritional indices and body composition parameters including sarcopenia in patients treated with radiotherapy for urothelial carcinoma of the bladder. Urol Oncol. 2019;37(6):372-9.
373. Takama T, Okano K, Kondo A, Akamoto S, Fujiwara M, Usuki H, et al. Predictors of postoperative complications in elderly and oldest old patients with gastric cancer. Gastric Cancer. 2015;18(3):653-61.

374. Tei M, Ikeda M, Haraguchi N, Takemasa I, Mizushima T, Ishii H, et al. Risk factors for postoperative delirium in elderly patients with colorectal cancer. Surgical endoscopy. 2010;24(9):2135-9.
375. Tei M, Wakasugi M, Kishi K, Tanemura M, Akamatsu H. Incidence and risk factors of postoperative delirium in elderly patients who underwent laparoscopic surgery for colorectal cancer. Int J Colorectal Dis. 2016;31(1):67-73.
376. Tominaga T, Takeshita H, Takagi K, Kunizaki M, To K, Abo T, et al. E-PASS score as a useful predictor of postoperative complications and mortality after colorectal surgery in elderly patients. Int J Colorectal Dis. 2016;31(2):217-25.
377. Toya Y, Endo M, Nakamura S, Akasaka R, Yanai S, Kawasaki K, et al. Long-term outcomes and prognostic factors with non-curative endoscopic submucosal dissection for gastric cancer in elderly patients aged >/= 75 years. Gastric Cancer. 2018.
378. Ueno D, Matsumoto H, Kubota H, Higashida M, Akiyama T, Shiotani A, et al. Prognostic factors for gastrectomy in elderly patients with gastric cancer. World J Surg Oncol. 2017;15(1):59.
379. Watanabe M, Iwatsuki M, Iwagami S, Ishimoto T, Baba Y, Baba H. Prognostic nutritional index predicts outcomes of gastrectomy in the elderly. World J Surg. 2012;36(7):1632-9.
380. Watanabe I, Kanauchi N, Watanabe H. Preoperative prognostic nutritional index as a predictor of outcomes in elderly patients after surgery for lung cancer. Japanese journal of clinical oncology. 2018;48(4):382-7.
381. Yoshimatsu K, Yokomizo H, Yano Y, Okayama S, Sakuma A, Satake M, et al. [Preoperative Prognostic Nutritional Index in Elderly Patients Over 80 Years Old Who Underwent Curative Resection for Colorectal Cancer]. Gan To Kagaku Ryoho. 2016;43(12):1529-31.
382. Zauderer MG, Sima CS, Korc-Grodzicki B, Kris MG, Krug LM. Toxicity of initial chemotherapy in older patients with lung cancers. J Geriatr Oncol. 2013;4(1):64-70.
383. Zhou YC, Chen LL, Xu HB, Sun Q, Zhang Q, Cai HF, et al. Aging-related prognosis analysis of definitive radiotherapy for very elderly esophageal cancer. Cancer Med. 2018;7(5):1837-44.
384. Girre V, Falcou M-C, Gisselbrecht M, Gridel G, Mosseri V, Bouleuc C, et al. Does a geriatric oncology consultation modify the cancer treatment plan for elderly patients? The journals of gerontology Series A, Biological sciences and medical sciences. 2008;63(7):724-30.
385. Rajasekaran T, Tan T, Ong WS, Koo KN, Chan L, Poon D, et al. Comprehensive Geriatric Assessment (CGA) based risk factors for increased caregiver burden among elderly Asian patients with cancer. J Geriatr Oncol. 2016;7(3):211-8.
386. Aparicio T, Jouve JL, Teillet L, Gargot D, Subtil F, Le Brun-Ly V, et al. Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients. J Clin Oncol. 2013;31(11):1464-70.
387. Falandry C, Weber B, Savoye AM, Tinquaut F, Tredan O, Sevin E, et al. Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial. Ann Oncol. 2013;24(11):2808-13.
388. Ulibarri J, gonzalez-Madroño A, Villar N, González P, González B, Mancha A, et al. CONUT: A tool for Controlling Nutritional Status. First validation in a hospital population. Nutrición hospitalaria : organo oficial de la Sociedad Española de Nutrición Parenteral y Enteral. 2005;20:38-45.
389. Aziz EF, Javed F, Pratap B, Musat D, Nader A, Pulimi S, et al. Malnutrition as assessed by nutritional risk index is associated with worse outcome in patients admitted with acute decompensated heart failure: an ACAP-HF data analysis. Heart Int. 2011;6(1):e2-e.
390. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. The American journal of clinical nutrition. 2005;82(4):777-83.
391. Bourdel-Marchasson I, Blanc-Bisson C, Doussau A, Germain C, Blanc J-F, Dauba J, et al. Nutritional advice in older patients at risk of malnutrition during treatment for chemotherapy: a two-year randomized controlled trial. PloS one. 2014;9(9):e108687.

392. Li J, Xu R, Hu DM, Zhang Y, Gong TP, Wu XL. Prognostic Nutritional Index Predicts Outcomes of Patients after Gastrectomy for Cancer: A Systematic Review and Meta-Analysis of Nonrandomized Studies. Nutrition and cancer. 2019;71(4):557-68.
393. Sun G, Li Y, Peng Y, Lu D, Zhang F, Cui X, et al. Impact of the preoperative prognostic nutritional index on postoperative and survival outcomes in colorectal cancer patients who underwent primary tumor resection: a systematic review and meta-analysis. International journal of colorectal disease. 2019;34(4):681-9.
394. Wang X, Wang Y. The prognostic nutritional index is prognostic factor of gynecological cancer: A systematic review and meta-analysis. International journal of surgery (London, England). 2019;67:79-86.
395. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer treatment reviews. 2013;39(5):534-40.
396. Benítez Brito N, Suárez Llanos JP, Fuentes Ferrer M, Oliva García JG, Delgado Brito I, Pereyra-García Castro F, et al. Relationship between Mid-Upper Arm Circumference and Body Mass Index in Inpatients. PloS one. 2016;11(8):e0160480-e.
397. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: A new category of obesity in the elderly. Nutrition, Metabolism and Cardiovascular Diseases. 2008;18(5):388-95.
398. Prentice AM, Jebb SA. Beyond body mass index. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2001;2(3):141-7.
399. Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc. 2011;12(6):403-9.
400. Isautier JMJ, Bosnic M, Yeung SSY, Trappenburg MC, Meskers CGM, Whittaker AC, et al. Validity of Nutritional Screening Tools for Community-Dwelling Older Adults: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc. 2019;20(10):1351.e13-.e25.
401. Power L, Mullally D, Gibney ER, Clarke M, Visser M, Volkert D, et al. A review of the validity of malnutrition screening tools used in older adults in community and healthcare settings - A MaNuEL study. Clin Nutr ESPEN. 2018;24:1-13.
402. GOV.UK. UK National Screening Committee: Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. In: England PH, editor. London: GOV; 2015.
403. Guyonnet S, Rolland Y. Screening for Malnutrition in Older People. Clinics in geriatric medicine. 2015;31(3):429-37.
404. Muscaritoli M, Krznaric Z, Singer P, Barazzoni R, Cederholm T, Golay A, et al. Effectiveness and efficacy of nutritional therapy: A systematic review following Cochrane methodology. Clin Nutr. 2017;36(4):939-57.
405. DeFrank JT, Barclay C, Sheridan S, Brewer NT, Gilliam M, Moon AM, et al. The psychological harms of screening: the evidence we have versus the evidence we need. Journal of general internal medicine. 2015;30(2):242-8.
406. Higgins JPT, Green, S. (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [online] Available at: www.handbook.cochrane.org: The Cochrane Collaboration. 2011.
407. Bullock A, Greenley, S., McKenzie, G., Patterson, M., Johnson, M.J. Patient, family and carers experiences of nutritional screening: a systematic review CDR42019140859 [online]: PROSPERO; 2019 [Available from: Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019140859.
408. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc. 2016;104(3):240-3.
409. Covidence systematic review software. [online] Available at: www.covidence.org: Veritas Health Innovation.
410. Pace R, Pluye P, Bartlett G, Macaulay AC, Salsberg J, Jagosh J, et al. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. International journal of nursing studies. 2012;49(1):47-53.

411. Sutton A, Clowes M, Preston L, Booth A. Meeting the review family: exploring review types and associated information retrieval requirements. Health Info Libr J. 2019;36(3):202-22.
412. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. 2008.
413. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12:181.
414. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008;8:45.
415. Cawood AL, Elia M, Sharp SK, Stratton RJ. Malnutrition self-screening by using MUST in hospital outpatients: validity, reliability, and ease of use. Am J Clin Nutr. 2012;96(5):1000-7.
416. Cawood AL, Walters ER, Sharp SKE, Elia M, Stratton RJ. 'Self-screening' for malnutrition with an electronic version of the Malnutrition Universal Screening Tool ('MUST') in hospital outpatients: concurrent validity, preference and ease of use. Br J Nutr. 2018;120(5):528-36.
417. Di Bella A, Blake C, Young A, Pelecanos A, Brown T. Reliability of Patient-Led Screening with the Malnutrition Screening Tool: Agreement between Patient and Health Care Professional Scores in the Cancer Care Ambulatory Setting. J Acad Nutr Diet. 2018;118(6):1065-71.
418. Tammam JD, Gardner L, Hickson M. Validity, reliability and acceptability of the Imperial Nutritional Screening System (INSYST): a tool that does not require the body mass index. J Hum Nutr Diet. 2009;22(6):536-44.
419. Callen B. Understanding nutritional health in older adults. A pilot study. Journal of gerontological nursing. 2004;30(1):36-43.
420. Kroner A, Stoll H, Spichiger E. [Malnutrition and weight loss - nurse assessment of nutritional status and counselling: experiences of patients with newly diagnosed or relapsed cancer]. Pflege. 2012;25(2):85-95.
421. Reimer H, Keller H, Tindale J. Learning you are "at risk": seniors' experiences of nutrition risk screening. Eur J Ageing. 2012;9(1):81-9.
422. Hamirudin AH, Charlton, K., Walton, K., Bonney, A., Albert, G., Hodgkins, A., Ghosh, A., Potter, J., Milosavljevic, M., Dalley, A. IMPLEMENTATION OF NUTRITION SCREENING FOR OLDER ADULTS IN GENERAL PRACTICE: PATIENT PERSPECTIVES INDICATE ACCEPTABILITY. J Aging Res Clin Practice. 2016;5(1):7-13.
423. Balstad TR, Bye A, Jenssen CR, Solheim TS, Thoresen L, Sand K. Patient interpretation of the Patient-Generated Subjective Global Assessment (PG-SGA) Short Form. Patient Prefer Adherence. 2019;13:1391-400.
424. Harris PS, Payne L, Morrison L, Green SM, Ghio D, Hallett C, et al. Barriers and facilitators to screening and treating malnutrition in older adults living in the community: a mixed-methods synthesis. BMC Fam Pract. 2019;20(1):100.
425. Omidvari AH, Vali Y, Murray SM, Wonderling D, Rashidian A. Nutritional screening for improving professional practice for patient outcomes in hospital and primary care settings. The Cochrane database of systematic reviews. 2013(6):Cd005539.
426. Woolf SH, Harris R. The harms of screening: new attention to an old concern. Jama. 2012;307(6):565-6.
427. Shickle D, Chadwick R. The ethics of screening: is 'screeningitis' an incurable disease? J Med Ethics. 1994;20(1):12-8.
428. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-95.
429. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough? Field Methods - FIELD METHOD. 2006;18:59-82.
430. Hoddinott P, Pollock A, O'Cathain A, Boyer I, Taylor J, MacDonald C, et al. How to incorporate patient and public perspectives into the design and conduct of research. F1000Res. 2018;7:752-.

431. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. Cmaj. 2005;173(5):489-95.
432. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
433. NIHR. Good Clinical Practice (GCP) [online]: National Institute for Health Research; 2019 [cited 2019 28th November]. Available from: https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm.
434. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49.
435. van Smeden M, de Groot JAH, Moons KGM, Collins GS, Altman DG, Eijkemans MJC, et al. No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. BMC Medical Research Methodology. 2016;16(1):163.
436. van Smeden M, Moons KG, de Groot JA, Collins GS, Altman DG, Eijkemans MJ, et al. Sample size for binary logistic prediction models: Beyond events per variable criteria. Statistical Methods in Medical Research. 2019;28(8):2455-74.
437. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med. 2000;19(8):1059-79.
438. Woolf B. On estimating the relation between blood group and disease. Ann Hum Genet. 1955;19(4):251-3.
439. Agresti A. On logit confidence intervals for the odds ratio with small samples. Biometrics. 1999;55(2):597-602.
440. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009;338:b2393.
441. NVivo. NVivo [online]: NVivo; 2019 [cited 2019 14th November]. Available from: https://www.qsrinternational.com/nvivo/what-is-nvivo.
442. O'Connor C, Joffe H. Intercoder Reliability in Qualitative Research: Debates and Practical Guidelines. International Journal of Qualitative Methods. 2020;19:1609406919899220.
443. WMA. WMA declaraion of Helsinki - Ethical principles for medical research involving human subjects [online]: World Medical Association; 2018 [cited 2019 19th November]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.
444. Jubb AM. Palliative care research: trading ethics for an evidence base. Journal of Medical Ethics. 2002;28(6):342-6.
445. Fine PG. Maximizing Benefits and Minimizing Risks in Palliative Care Research That Involves Patients Near the End of Life. Journal of Pain and Symptom Management. 2003;25(4):S53-S62.
446. Fine PG, Peterson D. Caring about what dying patients care about caring. J Pain Symptom Manage. 2002;23(4):267-8.
447. HCPC. Standards of conduct, performance and ethics [online]: Health and Care Professions Council 2019 [cited 2019 18th November]. Available from: https://www.hcpc-uk.org/standards/standards-of-conduct-performance-and-ethics/.
448. WHO. Events as the happen: Rolling updates on coronavirus disease (COVID-19) [online] Available at: www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen: World Health Organisation; 2020 [01 April 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen.
449. GOV. Coronavirus [online] Available at: www.gov.uk/coronavirus2020 [
450. CEBM. COVID-19: Admissions to Hospital - Update [online] Available at: www.cebm.net/covid-19/covid-19-uk-hospital-admissions/: The Centre for Evidence-based Medicine; 2020 [
451. NHS. COVID-19 Hospital Activity [online] Available at: www.england.nhs.uk/statistics/statistical-work-areas/covid-19-hospital-activity/ 2020 [

452. BMA. The hidden impact of COVID-19 on patient care in the NHS in England. In: Association BM, editor. [online] Available at: www.bma.org.uk/media/2841/the-hidden-impact-of-covid_web-pdf.pdf2020.
453. Alsiri NF, Alhadhoud MA, Palmer S. The impact of the COVID-19 on research. J Clin Epidemiol. 2021;129:124-5.
454. Giannakoulis VG, Papoutsi E, Siempos, II. Effect of Cancer on Clinical Outcomes of Patients With COVID-19: A Meta-Analysis of Patient Data. JCO Glob Oncol. 2020;6:799-808.
455. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol. 2020;21(8):1023-34.
456. Sun S, Folarin AA, Ranjan Y, Rashid Z, Conde P, Stewart C, et al. Using Smartphones and Wearable Devices to Monitor Behavioral Changes During COVID-19. J Med Internet Res. 2020;22(9):e19992.
457. Ammar A, Brach M, Trabelsi K, Chtourou H, Boukhris O, Masmoudi L, et al. Effects of COVID-19 Home Confinement on Eating Behaviour and Physical Activity: Results of the ECLB-COVID19 International Online Survey. Nutrients. 2020;12(6).
458. Herle M, Smith AD, Bu F, Steptoe A, Fancourt D. Trajectories of eating behavior during COVID-19 lockdown: Longitudinal analyses of 22,374 adults. Clin Nutr ESPEN. 2021;42:158-65.
459. Pierce M, Hope H, Ford T, Hatch S, Hotopf M, John A, et al. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. Lancet Psychiatry. 2020;7(10):883-92.
460. Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y. A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. Gen Psychiatr. 2020;33(2):e100213.
461. Morley JE, Kalantar-Zadeh K, Anker SD. COVID-19: a major cause of cachexia and sarcopenia? J Cachexia Sarcopenia Muscle. 2020;11(4):863-5.
462. Morley JE, Vellas B. Editorial: COVID-19 and Older Adults. J Nutr Health Aging. 2020;24(4):364-5.
463. Anker MS, Landmesser U, von Haehling S, Butler J, Coats AJS, Anker SD. Weight loss, malnutrition, and cachexia in COVID-19: facts and numbers. J Cachexia Sarcopenia Muscle. 2021;12(1):9-13.
464. Kirwan R, McCullough D, Butler T, Perez de Heredia F, Davies IG, Stewart C. Sarcopenia during COVID-19 lockdown restrictions: long-term health effects of short-term muscle loss. Geroscience. 2020;42(6):1547-78.
465. Gruther W, Benesch T, Zorn C, Paternostro-Sluga T, Quittan M, Fialka-Moser V, et al. Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. J Rehabil Med. 2008;40(3):185-9.
466. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.
467. Iacobucci G. Cancer trial recruitment fell by 60% last year during pandemic. Bmj. 2021;375:n3044.
468. Richardson SJ, Carroll CB, Close J, Gordon AL, O'Brien J, Quinn TJ, et al. Research with older people in a world with COVID-19: identification of current and future priorities, challenges and opportunities. Age and Ageing. 2020;49(6):901-6.
469. Kalpakidou AK, Todd C, Omar RZ, Keeley V, Griffiths J, Spencer K, et al. Study recruitment factors in advanced cancer: the Prognosis in Palliative care Study II (PiPS2) - a multicentre, prospective, observational cohort project. BMJ Support Palliat Care. 2021.
470. McMillan SC, Weitzner MA. Methodologic issues in collecting data from debilitated patients with cancer near the end of life. Oncol Nurs Forum. 2003;30(1):123-9.
471. Chaiviboontham S. Recruitment and retention challenges in research of palliative care in patients with advanced cancer. Progress in Palliative Care. 2011;19(4):185-8.

472. Hanson LC, Bull J, Wessell K, Massie L, Bennett RE, Kutner JS, et al. Strategies to support recruitment of patients with life-limiting illness for research: the Palliative Care Research Cooperative Group. J Pain Symptom Manage. 2014;48(6):1021-30.
473. Witham MD, McMurdo ME. How to get older people included in clinical studies. Drugs Aging. 2007;24(3):187-96.
474. UnitedNations. World Population Ageing 2015. In: Nations U, editor. New York: Department of Ecomonic and Social Affairs Population Division; 2015.
475. Townsley CA, Chan KK, Pond GR, Marquez C, Siu LL, Straus SE. Understanding the attitudes of the elderly towards enrolment into cancer clinical trials. BMC Cancer. 2006;6:34.
476. Liljas AEM, Walters K, Jovicic A, Iliffe S, Manthorpe J, Goodman C, et al. Strategies to improve engagement of 'hard to reach' older people in research on health promotion: a systematic review. BMC Public Health. 2017;17(1):349.
477. McMurdo MET, Roberts H, Parker S, Wyatt N, May H, Goodman C, et al. Improving recruitment of older people to research through good practice. Age and Ageing. 2011;40(6):659-65.
478. Schron EB, Wassertheil-Smoller S, Pressel S. Clinical trial participant satisfaction: survey of SHEP enrollees. SHEP Cooperative Research Group. Systolic Hypertension in the Elderly Program. Journal of the American Geriatrics Society. 1997;45(8):934-8.
479. Yuval R, Uziel K, Gordon N, Merdler A, Khader N, Karkabi B, et al. Perceived benefit after participating in positive or negative/neutral heart failure trials: the patients' perspective. Eur J Heart Fail. 2001;3(2):217-23.
480. Rodríguez-Torres E, González-Pérez MM, Díaz-Pérez C. Barriers and facilitators to the participation of subjects in clinical trials: An overview of reviews. Contemporary Clinical Trials Communications. 2021;23:100829.
481. Stone PC, Gwilliam B, Keeley V, Todd C, Kelly LC, Barclay S. Factors affecting recruitment to an observational multicentre palliative care study. BMJ Supportive & Palliative Care. 2013;3(3):318.
482. Julien JP, Combe C, Lasseur C. Subjective global assessment of nutrition a useful diagnostic tool for nurses? Edtna erca j. 2001;27(4):193-6.
483. Correira Pereira MA, Santos CA, Almeida Brito J, Fonseca J. Scored Patient-Generated Subjective Global Assessment, albumin and transferrin for nutritional assessment of gastrostomy fed head or neck cancer patients. Nutr Hosp. 2014;29(2):420-6.
484. Ida S, Kaneko R, Murata K. SARC-F for Screening of Sarcopenia Among Older Adults: A Meta-analysis of Screening Test Accuracy. J Am Med Dir Assoc. 2018;19(8):685-9.
485. Sales M, Levinger P, Polman R. Relationships between self perceptions and physical activity behaviour, fear of falling, and physical function among older adults. European Review of Aging and Physical Activity. 2017;14(1):17.
486. Hadjistavropoulos T, Delbaere K, Fitzgerald TD. Reconceptualizing the role of fear of falling and balance confidence in fall risk. J Aging Health. 2011;23(1):3-23.
487. Delbaere K, Crombez G, Vanderstraeten G, Willems T, Cambier D. Fear-related avoidance of activities, falls and physical frailty. A prospective community-based cohort study. Age Ageing. 2004;33(4):368-73.
488. Yee XS, Ng YS, Allen JC, Latib A, Tay EL, Abu Bakar HM, et al. Performance on sit-to-stand tests in relation to measures of functional fitness and sarcopenia diagnosis in community-dwelling older adults. European Review of Aging and Physical Activity. 2021;18(1):1.
489. Porporato PE. Understanding cachexia as a cancer metabolism syndrome. Oncogenesis. 2016;5(2):e200-e.
490. Small N, Bower P, Chew-Graham CA, Whalley D, Protheroe J. Patient empowerment in long-term conditions: development and preliminary testing of a new measure. BMC Health Services Research. 2013;13(1):263.
491. Correia M. Patient Empowerment on the Fight Against Malnutrition. JPEN Journal of parenteral and enteral nutrition. 2018;42(4):672-4.

492. Zhong X, Zimmers TA. Sex Differences in Cancer Cachexia. Curr Osteoporos Rep. 2020;18(6):646-54.
493. Skipworth RJE, Stewart GD, Dejong CHC, Preston T, Fearon KCH. Pathophysiology of cancer cachexia: Much more than host–tumour interaction? Clinical Nutrition. 2007;26(6):667-76.
494. Gingrich A, Volkert D, Kiesswetter E, Thomanek M, Bach S, Sieber CC, et al. Prevalence and overlap of sarcopenia, frailty, cachexia and malnutrition in older medical inpatients. BMC Geriatrics. 2019;19(1):120.
495. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2001;56(3):M146-M57.
496. Burke S, Wurz A, Bradshaw A, Saunders S, West MA, Brunet J. Physical Activity and Quality of Life in Cancer Survivors: A Meta-Synthesis of Qualitative Research. Cancers (Basel). 2017;9(5):53.
497. Reid J, McKenna H, Fitzsimons D, McCance T. The experience of cancer cachexia: A qualitative study of advanced cancer patients and their family members. International journal of nursing studies. 2009;46(5):606-16.
498. Dominguez Castro P, Reynolds CM, Kennelly S, Clyne B, Bury G, Hanlon D, et al. General practitioners' views on malnutrition management and oral nutritional supplementation prescription in the community: A qualitative study. Clin Nutr ESPEN. 2020;36:116-27.
499. Johnson MJ, Fallon M. Chronic breathlessness: time for Cinderella to go to the ball! Eur Respir J. 2018;52(3).
500. Hopkinson J, Wright D, Corner J. Exploring the experience of weight loss in people with advanced cancer. J Adv Nurs. 2006;54(3):304-12.
501. Gysels M, Higginson IJ. Access to services for patients with chronic obstructive pulmonary disease: the invisibility of breathlessness. J Pain Symptom Manage. 2008;36(5):451-60.
502. Cooper C, Burden ST, Cheng H, Molassiotis A. Understanding and managing cancer-related weight loss and anorexia: insights from a systematic review of qualitative research. J Cachexia Sarcopenia Muscle. 2015;6(1):99-111.
503. Payne L, Harris P, Ghio D, Slodkowska-Barabasz J, Sutcliffe M, Kelly J, et al. Beliefs about inevitable decline among home-living older adults at risk of malnutrition: a qualitative study. J Hum Nutr Diet. 2020;33(6):841-51.
504. Biskup E, Vetter M, Wedding U. Fighting diagnostic and therapeutic nihilism in the elderly with cancer. Annals of Palliative Medicine. 2019;9(3):1324-32.
505. Swaminathan D, Swaminathan V. Geriatric oncology: problems with under-treatment within this population. Cancer Biol Med. 2015;12(4):275-83.
506. Biller J, Love BB. Nihilism and stroke therapy. Stroke. 1991;22(9):1105-7.
507. Barnes-Harris MM, Daniel S, Venkateswaran C, Hutchinson A, Johnson MJ. How Physicians in South India Recognize, Assess, and Manage People with Chronic Breathlessness Syndrome: A Thematic Analysis. Indian J Palliat Care. 2021;27(1):54-61.
508. Amano K, Baracos VE, Hopkinson JB. Integration of palliative, supportive, and nutritional care to alleviate eating-related distress among advanced cancer patients with cachexia and their family members. Critical Reviews in Oncology/Hematology. 2019;143:117-23.
509. ONS. Mortality statistics - underlying, cause, sex and age. In: Statistics OfN, editor. [online] Available at: https://www.nomisweb.co.uk/query/construct/submit.asp?menuopt=201: ONS; 2020.
510. Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. J Cachexia Sarcopenia Muscle. 2016;7(5):512-4.
511. Lim S, Brown JL, Washington TA, Greene NP. Development and progression of cancer cachexia: Perspectives from bench to bedside. Sports Medicine and Health Science. 2020;2(4):177-85.
512. von Haehling S, Anker MS, Anker SD. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. J Cachexia Sarcopenia Muscle. 2016;7(5):507-9.

513. Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J, et al. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. Annals of oncology : official journal of the European Society for Medical Oncology. 2014;25(8):1492-9.
514. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. Eur J Intern Med. 2016;31:3-10.
515. Wallis SJ, Wall J, Biram RWS, Romero-Ortuno R. Association of the clinical frailty scale with hospital outcomes. QJM: An International Journal of Medicine. 2015;108(12):943-9.
516. Basic D, Shanley C. Frailty in an Older Inpatient Population:Using the Clinical Frailty Scale to Predict Patient Outcomes. Journal of Aging and Health. 2015;27(4):670-85.
517. Cruz-Jentoft AJ, Kiesswetter E, Drey M, Sieber CC. Nutrition, frailty, and sarcopenia. Aging clinical and experimental research. 2017;29(1):43-8.
518. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, et al. Physical activity and exercise as countermeasures to physical frailty and sarcopenia. Aging clinical and experimental research. 2017;29(1):35-42.
519. Van Ancum J, Meskers C, Reijnierse E, Yeung S, Jonkman N, Trappenburg M, et al. Lack of Knowledge Contrasts the Willingness to Counteract Sarcopenia Among Community-Dwelling Adults. Journal of Aging and Health. 2019;32:089826431985284.
520. Kress L, Aue T. The link between optimism bias and attention bias: A neurocognitive perspective. Neuroscience & Biobehavioral Reviews. 2017;80:688-702.
521. Weinstein ND. Unrealistic optimism about future life events. Journal of personality and social psychology. 1980;39:806-20.
522. Browning KK, Wewers ME, Ferketich AK, Otterson GA, Reynolds NR. The Self-regulation Model of Illness applied to smoking behavior in lung cancer. Cancer Nurs. 2009;32(4):E15-E25.
523. Katapodi MC, Dodd MJ, Lee KA, Facione NC. Underestimation of breast cancer risk: influence on screening behavior. Oncol Nurs Forum. 2009;36(3):306-14.
524. Ferrer R, Klein WM. Risk perceptions and health behavior. Curr Opin Psychol. 2015;5:85-9.
525. Tenkorang EY. Effect of knowledge and perceptions of risks on Ebola-preventive behaviours in Ghana. International Health. 2018;10(3):202-10.
526. Jacobson JD, Catley D, Lee HS, Harrar SW, Harris KJ. Health risk perceptions predict smoking-related outcomes in Greek college students. Psychol Addict Behav. 2014;28(3):743-51.
527. Craven DL, Lovell GP, Pelly FE, Isenring E. Community-Living Older Adults' Perceptions of Body Weight, Signs of Malnutrition and Sources of Information: a Descriptive Analysis of Survey Data. J Nutr Health Aging. 2018;22(3):393-9.
528. Castro PD, Reynolds C, Kennelly S, Clyne B, Bury G, Bradley C, et al. “Don’t Go Near The Word Malnutrition”; A qualitative study of community healthcare professionals and patients views on the term malnutrition. Clinical Nutrition ESPEN. 2020;40:592.
529. Lueg G, Wirth R, Kwiatkowski J, Rösler A, Jäger M, Gehrke I, et al. Low Self-Perception of Malnutrition in Older Hospitalized Patients. Clin Interv Aging. 2020;15:2219-26.
530. Reiss S, Levitan GW, Szyszko J. Emotional disturbance and mental retardation: diagnostic overshadowing. Am J Ment Defic. 1982;86(6):567-74.
531. Spruit MA, Vercoulen JH, Sprangers MAG, Wouters EFM. Fatigue in COPD: an important yet ignored symptom. Lancet Respir Med. 2017;5(7):542-4.
532. Winter J, McNaughton SA, Nowson CA. OLDER ADULTs ATTITUDES TO FOOD AND NUTRITION: A QUALITATIVE STUDY. Journal of Aging Research and Lifestyle. 2016.
533. Jones S, Howard L, Thornicroft G. 'Diagnostic overshadowing': worse physical health care for people with mental illness. Acta Psychiatr Scand. 2008;118(3):169-71.
534. Molloy R, Brand G, Munro I, Pope N. Seeing the complete picture: A systematic review of mental health consumer and health professional experiences of diagnostic overshadowing. J Clin Nurs. 2021.

535. Avgerinou C, Bhanu C, Walters K, Croker H, Liljas A, Rea J, et al. Exploring the Views and Dietary Practices of Older People at Risk of Malnutrition and Their Carers: A Qualitative Study. Nutrients. 2019;11(6):1281.
536. Hopkinson JB, Wright DNM, McDonald JW, Corner JL. The Prevalence of Concern About Weight Loss and Change in Eating Habits in People with Advanced Cancer. Journal of Pain and Symptom Management. 2006;32(4):322-31.
537. Rossi RE, Conte D, Massironi S. Diagnosis and treatment of nutritional deficiencies in alcoholic liver disease: Overview of available evidence and open issues. Dig Liver Dis. 2015;47(10):819-25.
538. Schcolnik-Cabrera A, Chávez-Blanco A, Domínguez-Gómez G, Dueñas-González A. Understanding tumor anabolism and patient catabolism in cancer-associated cachexia. Am J Cancer Res. 2017;7(5):1107-35.
539. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med. 2019;18(3):121-6.
540. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nature Medicine. 2019;25(12):1822-32.
541. Therakomen V, Petchlorlian A, Lakananurak N. Prevalence and risk factors of primary sarcopenia in community-dwelling outpatient elderly: a cross-sectional study. Scientific reports. 2020;10(1):19551-.
542. Kurose S, Nishikawa S, Nagaoka T, Kusaka M, Kawamura J, Nishioka Y, et al. Prevalence and risk factors of sarcopenia in community-dwelling older adults visiting regional medical institutions from the Kadoma Sarcopenia Study. Scientific Reports. 2020;10(1):19129.
543. Durrand J, Singh SJ, Danjoux G. Prehabilitation. Clin Med (Lond). 2019;19(6):458-64.
544. Lukez A, Baima J. The Role and Scope of Prehabilitation in Cancer Care. Seminars in Oncology Nursing. 2020;36(1):150976.
545. Forbes CC, Swan F, Greenley SL, Lind M, Johnson MJ. Physical activity and nutrition interventions for older adults with cancer: a systematic review. J Cancer Surviv. 2020;14(5):689-711.
546. Nuttall FQ. Body Mass Index: Obesity, BMI, and Health: A Critical Review. Nutrition Today. 2015;50(3):117-28.
547. Humphreys S. The unethical use of BMI in contemporary general practice. Br J Gen Pract. 2010;60(578):696-7.
548. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. BMJ. 2016;353:i2156.
549. Kroenke CH, Neugebauer R, Meyerhardt J, Prado CM, Weltzien E, Kwan ML, et al. Analysis of Body Mass Index and Mortality in Patients With Colorectal Cancer Using Causal Diagrams. JAMA Oncology. 2016;2(9):1137-45.
550. Greenlee H, Unger JM, LeBlanc M, Ramsey S, Hershman DL. Association between Body Mass Index and Cancer Survival in a Pooled Analysis of 22 Clinical Trials. Cancer Epidemiol Biomarkers Prev. 2017;26(1):21-9.
551. Bullock AF, Greenley SL, Patterson MJ, McKenzie GAG, Johnson MJ. Patient, family and carer experiences of nutritional screening: a systematic review. J Hum Nutr Diet. 2021;34(3):595-603.
552. Perry HB, Zulliger R, Rogers MM. Community health workers in low-, middle-, and high-income countries: an overview of their history, recent evolution, and current effectiveness. Annu Rev Public Health. 2014;35:399-421.
553. GOV.UK. Guidance: The Eatwell Guide Online: Public Health England; 2018 [cited 2022 27th January]. Available from: https://www.gov.uk/government/publications/the-eatwell-guide.
554. Rich JT, Neely JG, Paniello RC, Voelker CC, Nussenbaum B, Wang EW. A practical guide to understanding Kaplan-Meier curves. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010;143(3):331-6.

555. Balstad TR, Bye A, Jenssen CR, Solheim TS, Thoresen L, Sand K. Patient interpretation of the Patient-Generated Subjective Global Assessment (PG-SGA) Short Form. Patient Prefer Adherence. 2019;13:1391-400.

Appendices

Appendix 1: Original thesis aims and objectives

The original overarching aim of this thesis was to:

- Develop a single, clinically relevant screening tool, able to identify and distinguish between elements of malnutrition, sarcopenia, and cachexia in older adults with cancer.

Specific research questions identified from chapter one are:

1. What is the relationship between markers of malnutrition and clinical outcomes in older adults with cancer, in the published literature?
2. What are patients, their families, and carers experiences and views of nutritional screening, as identified in the published literature?
3. What are the experiences and views of older adults with cancer regarding screening for malnutrition, sarcopenia, and cachexia?
4. Which markers of malnutrition, sarcopenia, and cachexia used in screening tools are predictive of clinical outcomes in older adults with cancer?
5. What is the acceptability, and clinical utility, of a single screening tool, to detect malnutrition, sarcopenia, and cachexia, for older adults with cancer?

The research objectives, in response to each of these questions are:

1. To identify, synthesise, and critically appraise the published evidence regarding commonly used markers of nutritional status and clinical outcomes in older adults with cancer.
2. To identify, synthesise, and critically appraise the published evidence regarding patients, their families and carers views and experiences of nutritional risk screening.
3. To explore and understand patients experiences and views of the clinical assessment and management of malnutrition, sarcopenia, and cachexia.
4. To investigate the feasibility of conducting a subsequent adequately powered study to develop, refine, and test, a single, clinically relevant screening tool, able to identify and distinguish between elements of malnutrition, sarcopenia, and cachexia in older adults with cancer.
5. To explore the relationship between malnutrition, sarcopenia, and cachexia and clinical outcomes

6. To assess the statistical properties of the new tool as proof of concept
7. To explore the acceptability and feasibility of the new tool by patients and clinicians

Summary of changes to research questions required due to the COVID-19 pandemic

	Original research questions	**Amended research questions due to COVID-19**
Overarching research aim	Develop a single, clinically relevant screening tool, able to identify and distinguish between elements of malnutrition, sarcopenia, and cachexia in older adults with cancer	To determine the feasibility, clinical relevance, and patient acceptance and perceived benefit of a clinically relevant screening tool, able to identify and distinguish between elements of malnutrition, sarcopenia, and cachexia in older adults with cancer
Question One	What is the relationship between markers of malnutrition and clinical outcomes in older adults with cancer, in the published literature?	No change
Method for question	Systematic review of the published literature	No change
Question Two	What are patients, their families, and carers experiences and views of nutritional screening, as identified in the published literature?	No change
Method for question	Systematic review of the published literature	No change
Question Three	What are the experiences and views of older adults with cancer regarding screening for malnutrition, sarcopenia, and cachexia?	No change

Method for question	Patient participant interviews	No change
Question Four	Which markers of malnutrition, sarcopenia, and cachexia used in screening tools are predictive of clinical outcomes in older adults with cancer	Unable to address question
Method for question	Cohort study	Unable to address with cohort study due to interrupted ability to recruit in sufficient participant numbers
Question Five	What is the acceptability, and clinical utility, of a single screening tool, to detect malnutrition, cachexia, and sarcopenia, for older adults with cancer?	Unable to address question
Method for question	Cohort study	Unable to address with cohort study due to interrupted ability to recruit in sufficient participant numbers
Question Six		What is the prevalence and overlap of malnutrition, sarcopenia, and cachexia in a cohort of older adults with cancer?
Method for question		Cohort study

Appendix 2: Study protocol: Development, refinement and acceptability of a single clinical screening tool to detect Malnutrition, Sarcopenia and Cachexia in Older Adults with Cancer

Development, refinement and acceptability of a single clinical screening tool to detect Malnutrition, Sarcopenia and Cachexia in Older Adults with Cancer

Version: 2.5

Date: 11.07.2019

Name of Sponsor: University of Hull

Funder: Yorkshire Cancer Research

Funder Reference: YNA160

Sponsor

University of Hull will act as sponsor for the study.

Funding

This study is funded by Yorkshire Cancer Research, TRANSFORM project

Chief Investigator

Alex Bullock
Clinical Research Fellow (Nutrition)
Hull York Medical School
Allam Medical Building
The University of Hull
Hull, HU6 7RX

Co-Investigators

Professor Miriam Johnson
Professor of Palliative Medicine
Wolfson Palliative Care Research Centre
Hull York Medical School
Allam Medical Building
The University of Hull
Hull, HU6 7RX

Dr Lewis Paton
Research Fellow
Department of Health Sciences
Area 4, ARRC Building
University of York
YO10 5DD

Professor Mike Lind
Director of Research (Hull)
Professor of Oncology
Allam Medical Building
The University of Hull
Hull, HU6 7RX

Dr Gordon McKenzie
Clinical Research Fellow (Geriatric Oncology)
Hull York Medical School
Allam Medical Building
The University of Hull
Hull, HU6 7RX

Abbreviations and Glossary

MCASCO	Mini-CAchexia SCOre; cachexia screening tool consisting of anthropometric measures, blood parameters and questions regarding physical performance, anorexia and quality of life
SARC-F	Sarcopenia screening tool, consisting of 5 components; strength, assistance walking, chair rises, stair climbs and falls
MDT	Multi-Disciplinary Team
QCOH	Queens Centre for Oncology and Haematology
HUTH	Hull University Teaching Hospital NHS Trust
Malnutrition	Inadequate nutrition
Cachexia	A disease-related metabolic syndrome, leading to weight loss
Sarcopenia	Progressive skeletal muscle disorder, resulting in muscle-loss
Anorexia	Loss of appetite
AHP	Allied Health Professional; including dietitians, occupational therapists, physiotherapists and speech and language therapists.

Summary

Lay Summary

Older people are more likely to get cancer, but are less likely to cope with cancer treatments. Older people are also more likely to have problems with their eating, known as malnutrition, and problems keeping their muscles healthy, known as sarcopenia. Cancer may also cause weight loss and weaker muscles, knowns as cachexia. Because of these, older people with cancer have several reasons that make it harder for them to stay well, or cope with their cancer treatments. Checking for these problems involves completing questionnaires and simple tests of people's ability to complete everyday tasks. However these tests are time-consuming and include similar questions – and therefore may not be done at all. They are also not tailored to older people, making it hard to work out the problems for any individual. In addition, we do not know how people feel about being tested for these problems – especially so soon after a worrying diagnosis.

The aim of this study is to find out if we can test older people with cancer for eating problems, weak muscles or cancer-related weight loss all at the same time, in a way that is easy for patients and clinical teams to do.

We will ask up to 120 older people with cancer to complete standard questions about their eating, ability to carry out everyday tasks, and cancer-related weight loss. Simple measures of muscle health will also be taken. We will then look to see which parts of the tests overlap and what can be combined to form a short version to check for all three problems at the same time. We will also follow study participants up over 6 to 12 months to see how well they managed their cancer treatments, how well they are, and whether the test results can predict how well they do. Once we have developed the short tool, we will invite a small group (about 10) of older people with cancer to try the tool out with their dietitian or a member of their medical team.

We will also invite about 15 to 20 patient participants and about 5 to 10 clinicians to take part in an interview (patients or clinicians) or group discussion (clinicians) to find out their views and experiences of being asked/asking about these issues, and the tests involved.

At the end of the study, we will aim to have a short clinically usable test that can look for all three issues. This can then be tested in a larger study at a later date.

Background and Rationale

Malnutrition (inadequate nutrition [1]), cachexia (a disease-related metabolic state leading to weight loss [2]), and sarcopenia (age-related muscle loss [3]), are three conditions with similar symptoms, all of which are commonly associated with advanced age and disease. However, despite similar clinical appearances, these three conditions have different pathologies and treatments.

Malnutrition is thought to affect over 1.5 million people aged over 65 in the UK every year, with a third of people admitted to hospital aged over 65 at risk of malnutrition [4,5]. Malnutrition, results in reduced physical and mental function, and negatively predicts patients clinical outcomes, including mortality [1,6-7].

Rates of malnutrition are high in the cancer population, affecting between 14 and 67% of patients depending on diagnosis [8], as risk factors for malnutrition include; presence of

chronic disease, older age, use of anti-cancer therapies and tumour-related factors including obstruction, pain and dysphagia [9-12].

Nutritional screening for malnutrition is recommended for both hospital inpatients and outpatients, and Care Quality Commission regulations state that a patient's assessment should address 'risks related to people's nutrition and hydration needs' [13-14]. However, there is no consensus regarding the most appropriate tool to detect malnutrition. A recent review found 19 published screening tools for malnutrition [15]. A study comparing three of the most commonly used screening tools in cancer patients found that risk of malnutrition varied between 20 and 52%, depending on the tool used [16].

Alongside malnutrition, cachexia, which presents with weight loss, anorexia and reduced physical function [2], is thought to affect up to 50% of advanced cancer patients, and is associated with reduced patient survival times, and diminished quality of life [17]. Similarly, sarcopenia, an age-related, progressive muscle disorder, increases a patient's likelihood of falls, disability and mortality [3]. Despite their negative impact on patient outcomes, cachexia and sarcopenia are not routinely screened for, or managed in clinical practice. The 'SARC-F' screening tool and its associated algorithm for identifying sarcopenia [3], and Mini CAchexia SCOre (MASCO) [18] are validated for use in older cancer patients. However due to the time and equipment required to complete these tools, screening for these conditions in clinical practice is not routinely conducted.

Due to the increased prevalence of these three conditions in older people with cancer and availability of interventions, it is essential for these conditions are identified in older cancer patients, to ensure appropriate management. Due to the similarity in clinical characteristics between malnutrition, cachexia and sarcopenia, it is important that any screening tool used can distinguish between these distinct elements and is usable in daily clinical practice.

Therefore, there is a need for a simplified and clinically useful method of identifying components of malnutrition, cachexia and sarcopenia in older cancer patients, so that patient-centred care can be offered.

The overall aim of this study is to develop a single, clinically relevant screening tool, able to identify elements of malnutrition, cachexia and sarcopenia in older patients with cancer.

It is also important to consider the burdens alongside potential benefits of screening for these conditions, as screening can increase anxiety and distress if patients are positively diagnosed with a condition [19].Therefore this study will also explore the older cancer patient's experiences and view of the screening process, as well as the clinically utility of this tool in predicting adverse patient outcomes. Previous qualitative studies have been conducted regarding patients and clinicians experiences of malnutrition and cancer related weight loss [20]. However, to the best of our knowledge, no research has been conducted regarding cancer patients' experiences, understanding or impact of being screened for cachexia or sarcopenia, and minimal research has been conducted regarding understanding or impact of the screening process for malnutrition.

Aim and Objectives

Aim

The overall aim of this study is to develop a single, clinically relevant screening tool, able to identify elements of malnutrition, cachexia and sarcopenia in older patients with cancer.

Objectives

Primary objective

To develop a single screening tool for malnutrition, cachexia and sarcopenia

Secondary objectives

To gain an exploratory estimate of the prevalence of malnutrition, cachexia and sarcopenia in a cohort of older cancer patients

To explore the relationship between malnutrition, cachexia and sarcopenia and clinical outcomes

To explore statistical properties of the new tool as proof of concept

To explore patients' and clinicians' experience and views of clinical assessment and management of malnutrition, cachexia and sarcopenia

To explore the acceptability and feasibility of the new tool by patients and clinicians

To assess the feasibility of conducting a subsequent study to test the psychometric properties of the new tool.

Study Outcomes

Primary Outcome

Development of a single screening tool for malnutrition, cachexia and sarcopenia

Secondary Outcomes

Exploratory estimate of the prevalence of malnutrition, cachexia and sarcopenia

Exploration of the impact of diagnoses of malnutrition, cachexia and sarcopenia (gold-standard measures) on clinical outcomes; survival, hospital admissions, length of stay, anticancer treatment adherence and treatment toxicity

Patient and clinician experiences and views of the clinical assessment of malnutrition, cachexia and sarcopenia

Exploration of acceptability and feasibility of use of a single screening tool for malnutrition, cachexia and sarcopenia

Preliminary statistical properties of the streamlined tool

Recruitment rates, data quality for and time taken to complete all three screening tools in order to inform the design and feasibility of a subsequent psychometric properties study.

Study Design

This is a two-stage mixed-methods, single centre observational study. Step One is an exploratory observational cohort study. Participants receiving inpatient and outpatient care at the Queens Centre for Oncology and Haematology (QCOH) will be screened for malnutrition, cachexia and sarcopenia using the SARC-F, MCASCO and nutritional screening questions and assessments. The results will be used to produce a single, shortened screening tool to detect the three conditions simultaneously. Clinical outcome data will be collected at baseline, and at 3, 6 and 12 months to explore the impact of diagnosis of these three conditions on participants' outcomes. The statistical properties of this tool will also be investigated. A subgroup of participants will also be invited to participate in in-depth qualitative interviews regarding their views and experiences of screening for these conditions.

Step Two will explore patients' and clinicians' opinion about the acceptability and feasibility of use of the singular tool in clinical practice. A small number of clinicians and patients will complete the single tool, and be invited for qualitative interviews regarding its use.

Step One: Prospective Observational Cohort Study with Qualitative Interviews

Study Participants and Setting

Eligible participants receiving inpatient or outpatient care at the Queens Centre for Oncology and Haematology, at the Hull University Teaching Hospital NHS Trust (HUTH) will be invited to participate if they meet the following criteria;

Participant eligibility

Inclusion criteria

- Receiving inpatient or outpatient care at QCOH;
- Aged 70 years or older; due to increased risk of malnutrition, cachexia and sarcopenia, likely comorbid status, and increased negative outcomes if affected by these conditions [2-3,5-6,18]. Half of all new cancer diagnoses are within this age group [21].
- MDT agreed diagnosis of one of the following cancers; lung, prostate, breast, colorectal, head and neck or upper-gastrointestinal cancers. These sites include the four most common cancer diagnoses; breast, prostate, lung and colorectal. Head and neck and upper gastrointestinal cancers can impact significantly on a patient's nutrition [16,21,22].
- Able to provide informed written or verbal consent

Exclusion Criteria

- Participants who are considered by the clinical team to be in the last few weeks of life;
- Participant unable to understand English well enough to provide fully informed consent, or comply with the study assessments, and suitable translation services are not available;
- Participants on other clinical trials will be assessed on a case-by-case basis

Participant recruitment: identification and consent

Patients attending the QCOH for outpatient clinic appointment for lung, prostate, breast, colorectal, head and neck or upper-gastrointestinal (UGI) cancers will be screened for eligibility. Similarly, patients admitted to the inpatient facilities will be screened for eligibility and approached, as appropriate, by a member of the clinical team.

A screening log will be kept to identify the proportion of patients approached that meet the study inclusion criteria. If a patient failed to meet the screening criteria, they may be rescreened on a subsequent occasion if their clinical status has changed (for example, the patient now has sufficient mental capacity to provide informed consent).

Interested patients be will be provided with a participant information sheet (PIS) and will be given the opportunity to discuss the study with a member of the research team. As the study is observational and low risk, participants may provide immediate informed consent if they wish to prevent the burden of return visits or appointments.

If participants are unable to provide *written* consent, *witnessed* (by a family member, friend or independent member of staff who is not part of research team) verbal consent can be provided.

Participants without capacity for consent will not be included within the study, as it is unlikely that they will be able to comply with study measures.

The consent form will include explicit optional consent for an interview.

Participants are free to withdraw from the study at any time without having to give a reason, and without jeopardising their clinical care. Data collected up until the point of withdrawal will continue to be used. Participants who withdraw from follow up will be asked if they are willing to allow the researchers access to their routinely recorded electronic clinical record data.

Study Procedures and Assessments

Data will be collected at baseline, at 3 months, 6 months and a year. An assessment schedule with corresponding measures required can be seen in Table 1 (4.2.6).

Baseline clinical and demographic measures

The following measures will be collected at baseline; age, sex, ethnicity, primary tumour site and stage of disease, cancer treatment, place of residence, social support, frailty measured using the 'Rockwood Clinical Frailty Scale', and comorbidities using the 'Charlson comorbidity index', see Appendix 1 for details. The majority of baseline demographics will be gained from patients' records.

Baseline screening

Screening for sarcopenia, malnutrition and cachexia will be conducted at baseline only. Baseline screening measures will be collected during a single contact, unless requested by the participant to pause the study measure and recommence, within 7 days, due to fatigue.

Cachexia

Cachexia will be screened for used the 'MCASCO' screening tool, a validated tool for identifying cachexia and its severity in cancer patients [18]. MCASCO uses three parameters; weight measures, blood parameters and questions. Participants weight history and bioelectrical impedance analysis (BIA) (a safe way of measuring how much muscle a person has, using a very low electrical signal which passes through the body [24]) will be used. Although MCASCO

requires blood parameters, we will not conduct additional tests but will note when they were missing. The most recent recorded blood test on the HUTH computer system Lorenzo will be used. Questions regarding physical performance, quality of life and anorexia will be asked. See Table 1 (4.2.6) for a summary of the assessment schedule and Appendix 2 for MCASCO questions.

Sarcopenia

Sarcopenia will be screened for using the SARC-F screening tool and associated algorithm [3]. The SARC-F consists of 5 questions designed to elicit self-reports from participants regarding characteristics of sarcopenia. The SARC-F is a validated tool for use in older patients in clinical settings [3,23]. See Table 1 (4.2.6) for a summary of the assessment schedule and appendix 3 for SARC-F questions.

If suspicion of sarcopenia is raised by the SARC-F tool, further assessments using either a hand-grip dynamometer or a chair stand test (timed rise 5 times from a seated position) will determine if a diagnosis of sarcopenia is probable. Further tests, a BIA and 'timed up and go' test (TUG) (rise from chair, walk 3 meters and return to seat) will confirm the severity of sarcopenia. Note, BIA measures will be available on all patients to use for this measure, as it forms part of the cachexia screening tool (see section 4.2.2.1), therefore repeat measures will not be conducted.

Malnutrition

A systematic review of the literature has been conducted as part of this PhD project to identify which screening tool is most appropriate to identify malnutrition in older cancer patients. This review provided information on the most appropriate markers of malnutrition to use in this study. All study measures will be non-invasive and will be specified before application for ethical approval. Table 1 (4.2.6) contains all measures for malnutrition screening that may be used.

Measures include; measures of patient's weight and height and mid-arm circumference (measurement of the mid-upper arm using a tape measure), hand-grip strength, and visual assessments of muscle wastage. Questions regarding diet, weight history, appetite, method of feeding, fluid intake, social support, clinical condition and symptoms, activities of daily living and functional ability. Blood parameters; we will not conduct additional tests.

Combined shortened clinical tool

Once sufficient data has been gained from the screening of patients using gold-standard measures for cachexia, sarcopenia and malnutrition, items from these screening tools will be used to produce a combined, and shortened screening tool for all three conditions. See Data Analysis section (6.2) for how this will be done.

Follow up measures

Participants will be asked to consent to collection of the following follow up measures for study purposes;

Patient survival;

Hospital admissions, reason for admission, and associated length of stays;

Prescription of anticancer treatments;

Adherence to prescribed anticancer treatments;

Toxicities to any anticancer treatments

Referral(s) to AHPs; Dietetic, Physiotherapist, Occupational Therapist or Speech Therapist services.

These outcomes will be used to explore the predictive values of diagnoses of malnutrition, cachexia and sarcopenia on patient outcomes. These outcomes will be collected at four time points during the study; baseline, 3 months post baseline, 6 months post baseline and 12 months post baseline. These follow up measures will be collected from patients' records as are all available on HUTH computer system Lorenzo, or the oncology information system ARIA.

Feasibility
As this study also aims to explore the feasibility of a subsequent study large enough to test the psychometric properties of the new short combined tool, we will also measure;

Recruitment rates;

Retention rates;

Time to complete screening assessment;

Percentage of patients unable to complete aspects of the screening assessments;

Reasons participants are unable to complete aspects of the screening assessment

Qualitative interviews

Sampling frame
Participants who have consented to participate in interview at study enrolment will form the sampling pool. Purposive sampling, according to age within the age bracket of ≥70 years; diagnosis and stage of the disease; presence or absence of a carer; and diagnosis of malnutrition, cachexia or sarcopenia by the screening tools, will be used to gain maximum variation. Step One will aim to recruit 10 to 15 patient participants for interview.

Methodological considerations
Material provided from the qualitative interviews will be used to inform the production of the singular screening tool. Participants' aspects of screening, including their understanding of the screening questions and opinions of the measures, will be used to complement the data provided by the observational cohort study. This will be conducted through sense checking of the screening tool questions.

Previous literature for qualitative research in nutrition and cancer has used a phenomenological approach, which is also appropriate here as we are investigating patient experience. Both inductive and deductive methodologies have also been employed, however as we are entering a relatively new area of qualitative research, it is appropriate to use an inductive approach to data analysis. This will allow generation of theories regarding participants' experiences of assessment, screening and the impact that screening may also have on them. As the field of enquiry is relatively narrow, we will use thematic analysis [26] which can nevertheless incorporate a phenomenological approach. As the researcher conducting the interviews (AB) is a Dietitian, a reflexivity journal will be kept with key notes and reflections made after each interview.

Data collection
Interviews will take place either at QCOH, the participant's home, or at the University of Hull, depending on the participant's preference.

All participant interviews will follow a topic guide to ensure consistency. The topic guide will be piloted prior to use and continue to be modified iteratively as the interviews progress.

Table 1: Assessment schedule

Time point	Screening tool	Data collection	Measures taken
Baseline	N/A	Baseline clinical Demographics	Age, sex, ethnicity, primary tumour site and stage of disease, cancer treatment, comorbidities, place of residence, and social support, 'Rockwood Clinical Frailty Scale', and 'Charlson Comorbidity Index score'. (See appendix 1 for questions)
	SARC-F	Initial screening;	5 questions regarding: strength, walking, chair rises, stair climbing and falls history (see appendix 2 for questions)
		Assessment;	Hand-grip dynamometer or chair stand test
		Confirmation of sarcopenia will be made through;	Bioelectrical Impedance Analysis (BIA) Note// BIA measures will be available on all patients to use in the measure, as it forms part of the cachexia screening tool
		Severity of sarcopenia confirmed with;	Measure of physical performance; timed-up-and-go (TUG) (rise from chair, walk 3 meters and return to seat).
	MCASCO	Initial screening;	12 questions regarding appetite, physical function, overall health (see appendix 3 for questions)
			Weight: reported weight loss, Bioelectrical impedance analysis (BIA) measure of lean body mass
			Blood parameters; albumin, haemoglobin, C-reactive protein (CRP) and lymphocyte count. Existing recent blood tests will be used.
	Malnutrition Screening tool	Initial screening; most appropriate method to be identified through systematic review;	Measures will include markers from published screening tools, a selection of; Measures of height and weight, mid-arm circumference (measurement of the mid-upper arm using a tape measure), hand-grip strength (using a hand-grip dynamometer), visual assessments of muscle wastage. Questions regarding diet, weight history, appetite, method of feeding, fluid intake, clinical condition and symptoms, activities of daily living and functional ability. Blood parameters; no additional tests will be conducted. Note// BIA and hand-grip measures will be available on all patients to use in the measure, as they form part of the cachexia and sarcopenia screening tools
Follow up Measures: -			
Baseline	NIL	Clinical outcomes	Hospital admission, length of stay, anticancer treatment adherence and treatment toxicity, AHP referral.
3 Months	NIL	Clinical outcomes	Survival, hospital admissions, length of stay, anticancer treatment adherence and treatment toxicity, AHP referral

6 Months	NIL	Clinical outcomes	Survival, hospital admissions, length of stay, anticancer treatment adherence and treatment toxicity, AHP referral
12 Months	NIL	Clinical outcomes	Survival, hospital admissions, length of stay, anticancer treatment adherence and treatment toxicity, AHP referral
Feasibility Assessment: -			
Feasibility assessment	Combined shortened clinical tool	Conducted by clinicians on a small cohort of patients	Identified elements of the above screening tools for malnutrition, cachexia and sarcopenia

Study Exit

- Participants who are too unwell to comply with the study requirements;
- Participants who withdraw consent for ongoing participation;
- Death

Withdrawal or Death

Participants are free to withdraw from the study at any time without their care being affected. Participants do not have to provide a reason for withdrawal. Data collected prior to withdrawal of consent will be used unless a participant withdraws consent for data to be used. Participants who withdraw from the screening measures will be asked if any prior consent to participate in an interview stands, and if researchers may still access routinely collected clinical record data. The following information will be collected on the withdrawal form;

- Date of withdrawal;
- Level of withdrawal (full/partial);
- Reason for withdrawal if participant is willing to provide

The following information will be collected in the event of death;

- Date of death;
- Cause of death

Statistical Considerations

Sample Size

We are anticipating collecting between 90 and 120 participants due to time and resource constraints of this project. Based on the work of Peduzzi et al. [27], allowing for 10 participants per item, and the anticipated prevalence of the outcomes in our sample, we anticipate that this sample size will produce valid exploratory statistical models using regression techniques. However, as this is a feasibility study, we are not performing a full validity analysis of the combined tool.

Power calculations will be considered post statistical analysis to allow inferences from these analyses to be drawn, as well as make inferences regarding future development of the tool.

Data Analysis

Quantitative data analysis

Production of a single, combined shortened clinical tool
Univariable and multivariable regression models will be built to analyse the relationship between items of the screening tools for cachexia, sarcopenia, and the markers of malnutrition, with the recorded participant outcomes. These models will also be informed by the published literature and patient interviews. The regression models will vary dependent upon the outcome being considered. The results of these models will be used to produce a simplified singular screening tool. Similarly, regression models will be used to analyse the secondary outcomes regarding diagnosis of the conditions against participant outcomes. Variables that have sufficient evidence of statistical significance, have been shown to be important in other published literature, have a plausible biological explanation or are noted as important by patients or clinicians during interviews at univariable analysis will be included in multivariate analysis models, and decisions regarding their inclusion in the final screening tool will also take into account results of the qualitative interviews.

Impact of participant screening tool diagnosis upon clinical outcomes
The relationship between the clinical phenotype (diet/muscle/cachexia) and survival, hospital admission, length of stay, anticancer treatment adherence and treatment toxicity will also be analysed. Patient outcome data will also be presented using Kaplan-Meier survival curves as appropriate.

Management of missing data
Missing data will be investigated using multiple imputation. Models will be re-run on the imputed data, and model coefficients will be compared with those from models fit to non-imputed data. Model coefficients will then be compared as a form of sensitivity analysis.

STATA statistical software will be used for data management and statistical analyses.

Qualitative data analysis
The first few interviews will be audiorecorded and transcribed verbatim by the researcher (AB) and thereafter by an approved transcriber. Data will be analysed using thematic analysis as proposed by Braun and Clarke [26]. This includes analysis in six stages; i) familiarisation with data using reading and re-reading of transcripts, ii) generation of initial codes, - two researchers will independently code line by line and then discuss to agree an initial code book following which all transcripts will be coded; iii) search for themes, iv) review themes, v)) define and name themes and vi) production of findings. NVivo qualitative data analysis software [25] will be used to store and manage data.

Step Two: Initial Testing of New Tool for Acceptability

Study Participants and Setting

Participant eligibility
Eligibility of patient participants and setting for Step Two will be as for Step One.

Eligible clinician participants employed at the QCOH, will be invited to participated if;

Inclusion criteria;
They are routinely involved in the screening of patients for malnutrition; (Nurses in inpatient and outpatient settings)

Are routinely involved in the assessment and treatment of patients for malnutrition; (Dietitians in inpatient and outpatient settings)

Participant recruitment
Recruitment of participants for Step Two will be as for Step One. Eligible clinicians will be invited to participate by a member of the clinical team. Interested clinicians will be provided with a separate participant information sheet (PIS), and will be given the opportunity to discuss the study with a member of the research team. Clinician participants may progress to immediate consent to minimise the time burden on busy clinicians, given the low risk nature of the study.

Study Procedures and Assessment
Clinicians will be asked to use the new tool on consented Step Two patient participants during a routine clinical assessment. Patient participants will be asked to participate in the clinical assessment by the research clinicians. Provision of participant information sheets and seeking consent will be conducted by the research clinicians.

Study measures
Baseline clinical and demographic measures of patient participants involved in Step Two will be collected at baseline, as for Step One.

Basic information regarding the clinician's profession will be collected, and information regarding the nature of the routine clinical assessment will also be collected; location (inpatient or outpatient), appointment type (new or follow up assessment).

Study measures regarding the feasibility of the tool will be collected;

Time taken to administer the tool;

Completion rates and data quality;

Both clinician and patient participants will be asked to partake in an interview (patients and clinicians) or a focus group (clinicians) to explore their experience and views of the new tool and whether any refinement of the tool is required.

Qualitative interviews and focus group

Sampling frame
As for Step One, patient participants who have consented to participate in the interview at study enrolment will form the sampling pool. Methods for sampling will be as for Step One. All clinician participants will be asked to participate in interviews and the focus group.

Methodological considerations
Methodological considerations for Step Two are as for Step One.

Data collection
Data collection for Step Two are as for Step One. In the event that the initial sense checking of the first five Step Two patient participant and first two to three clinician participant interviews indicates that a more in depth cognitive approach is needed, the analysis of Step Two interviews will be modified accordingly.

Study Exit
Participants who are too unwell to comply with the study requirements;

Participants who withdraw consent for ongoing participation

Withdrawal
Patient and clinician participants are free to withdraw from the study at any time without their care being affected. Participants do not have to provide a reason for withdrawal. Data

collected prior to withdrawal of consent will be used unless a participant withdraws consent for data to be used. Participants who withdraw from the screening measures will be asked if any prior consent to participate in an interview stands. The following information will be collected on the withdrawal form;

Date of withdrawal;

Level of withdrawal (full/partial);

Reason for withdrawal if participant is willing to provide

Statistical Considerations

Sample Size
We will aim to recruit up to 15 patient participants for Step Two. We anticipate that we will recruit between 5 and 10 clinicians. This sample size is empirical, with the aim of gaining sufficient initial experience of use of the tool in clinical practice to allow development and testing of initial clinical feasibility.

Data analysis

Quantitative data analysis
As Step Two aims to test the feasibility of use for the simplified tool, no statistical tests will be used. Simple descriptions of times to complete the tool, completion rates and data quality will also be presented.

Qualitative data analysis
Qualitative data will be analysed and managed as for Step One.

Confidentiality, Data Management and Archiving
All research data will be handled according to GDPR 2016/679 law. Data will be stored on a password protected computer located in secure University buildings and appropriately backed up. Participants will be allocated a unique study ID for data collection – therefore all data will be anonymised. A master index file linking the study ID with patient identifiable data for follow up data collection purposes will be held in a separate file in the password protected computer, accessible by authorised personnel only. An encrypted flash drive will be used if transportation of data is required.

As members of the research team are part of patient's clinical team, if any clinical or ethical concerns regarding patient care are raised during the study, upon discussion with a clinical supervisor (MJ/ML), confidentiality may be broken to raise these concerns with the patient's primary clinician.

Consent Forms
Consent forms will be given to the participant or their next of kin, a copy will be entered into the patient notes, and a copy will be retained by the researcher and stored in a locked cabinet separated from other study data or linked documents in the swipe care entry Wolfson Palliative Care Research Centre corridor in the Allam Medical Building, accessible by authorised personnel only.

Archiving
Study documents will be retained for 5 years in a locked cupboard in the passkey protected Wolfson Palliative Care Research Centre, accessible to authorised researchers only, and then destroyed. Audio files will be deleted from recorder and computer files following transcription.

At the End of the Study
At the end of the study, the Bioelectrical Impedance Analysis (BIA) scale and the Hand-Grip Dynamometer will be retained and stored by the research team for future ongoing research in this area.

Reporting and Dissemination
We aim to publish the results of this study in peer-reviewed journals as well as present at national and international conferences. All participants will be asked if they (or their family) would like to be sent a lay summary of the results of the study. If so, a newsletter with study findings will be posted to the participants address at the end of the study.

Ethical and Regulatory Considerations

Sharing of Screening Results
As this is an observation study, we are not aiming to affect or change participants' usual clinical management. Currently cachexia and sarcopenia are not screened for at HUTH, therefore results of these aspects of the study would not impact upon clinical decision making or participants' treatment. HUTH also follows its own protocol for nutritional risk screening, with the use of its 'nutritional risk screening tool'. For this, inpatients are screened daily for nutritional risk, and outpatients screened upon clinical concern. Due to these factors, the results for the gold-standard measures of sarcopenia and cachexia, and malnutrition will not be shared with the participants or clinicians. Lastly, the psychometric properties of the new tool will be unknown.

Although the clinician participants in Step Two will of necessity know the findings of the new tool, it will be made clear that the tool is not known yet to be valid and should not contribute to clinical decision making unless supported by other valid instruments/measures.

Patients without Capacity
Patients without capacity for consent will not be included within the study, as even though it is low risk and an observational study, it is unlikely that they will be able to comply with study measures.

Rapid Consent
As the study is observational and low risk, participants may provide immediate informed consent if they wish to participate in the study measures, as to prevent the burden of return visits or appointment (patients) or of further interruption of clinical practice (clinician). Participants may withdraw consent at any time.

Study Sponsorship
The University of Hull will act as sponsor for this study.

Project Management
The project will be managed under the governance of the Hull York Medical School Post Graduate School requirements. A Thesis Advisory Panel led by an independent chair and attended by the PhD candidate, primary and secondary supervisors and other methods experts as necessary and advised by an independent expert will monitor progress.

Appendix 3: CASP Checklist

CASP checklist questions for cohort studies questions (237)

1. Did the study address a clearly focused issue?
   Yes. Can't Tell. No
   Comments:

2. Was the cohort recruited in an acceptable way?
   Yes. Can't Tell. No
   Comments:

3. Was the exposure accurately measured to minimise bias?
   Yes. Can't Tell. No
   Comments:

4. Was the outcome accurately measured to minimise bis?
   Yes. Can't Tell. No
   Comments:

5. (a) Have the authors identified all important confounding factors?
   Yes. Can't Tell. No
   Comments:

5. (b) Have they taken into account of the confounding factors in the design and/or analysis?
   Yes. Can't Tell. No
   Comments:

6. (a) Was the follow up of subjects complete enough?
   Yes. Can't Tell. No
   Comments:

6. (b) Was the follow up of subjects long enough?
   Yes. Can't Tell. No
   Comments:

7. What are the results of this study?
   Comment:

8. How precise are the results?
   Comments:

9. Do you believe the results?
   Yes. Can't Tell. No
   Comments:

10. Can the results be applied to the local populations?
    Yes. Can't Tell. No
    Comments:

Appendix 4: Original data management plan

Planned data analysis

Quantitative data management

The collection of data, as outlined in appendix 1.0 will be made at baseline. Outcome measures, as outlined in section 4.0 will be collected at 3, 6 and 12 months.

To determine which measures are to be used in the single, reduced, screening tool, several analyses will be undertaken, including; regression analysis, survival analysis (including Kaplan-Meier analysis) and diagnostic test evaluation (including receiver operating characteristic (ROC) curve analysis). Data management and analyses will be performed in Stata version 15.1.

Regression analysis

Regression analysis enables the exploration of the relationships between outcomes of interest ('dependent variables') and predictors of interest ('independent variables').

For this study, the primary dependent variables will be presence (or absence) of the three conditions of interest (malnutrition, sarcopenia and cachexia). Secondary outcomes will be the patient outcome measures, such as survival, see section 4.0. The independent variables will be the markers of the three conditions, answers to the screening questions (e.g. body weight loss, biomarkers, as outlined in appendix 1.0), and available demographic data (see appendix 1.0).

For continuous dependant variables (e.g. length of hospital stay), linear regression will be used. Where the dependant variables are binary (e.g. diagnosis of sarcopenia) or categorical (e.g. category/severity of cachexia), logistic regression models will be used.

Univariate regression models will investigate the relationship between each independent variable and each dependent variable. The results from these analyses (i.e. effect sizes and tests of statistical significance), along with the results of a systematic review investigating the relationship between markers of malnutrition and patient outcomes, other relevant literature, and the results of the qualitative interviews, will be used to select independent variables for inclusion in multivariate analyses. On univariate analysis, a p-value of <0.20 will mark inclusion of a variable for multivariate analysis. Multivariate models will allow for confounding effects to be controlled for. A stepwise approach will then be used to develop the final screening tool, with inclusion criteria being $p<0.05$ on multivariate analysis, or variables which have been identified as relevant during literature review, or participant interviews and have sufficient justification for inclusion.

Survival analysis

Kaplan-Meier curves, used to manage time-to-event data (554), will be used to examine the relationship between the presence or absence of a diagnosis of malnutrition, sarcopenia or cachexia and participant survival outcomes. Depending on data quantity, additional curves, for independent markers, such as body mass index (BM) or percentage weight loss, may be dichotomised to examine their relationship with patient outcomes.

Diagnostic test evaluation

As many of the markers of the conditions being investigated, in particular malnutrition, have either disputed or arbitrary thresholds, Receiver Operating Characteristic (ROC) curves can be

used to select optimal thresholds for markers based upon their sensitivity and specificity. ROC curve analysis could be used, for markers such as percentage weight loss, BMI, hand-grip strength, to determine appropriate thresholds for predicting outcomes.

Qualitative data management

Interviews and focus groups will be voice-recorded and transcribed into Microsoft word documents. Voice-recordings will be anonymised to ensure confidentiality, will all identifying features removed. Recordings will be transcribed verbatim, including filler speech and conventions of dialogue, for full analysis of the context of the language and interaction between participants. Once transcribed, documents will be uploaded to NVivo; a qualitative data-analysis software tool.

A phenomenological approach, investigating participants lived experience, and their interpretations, will be used when analysing the data. The theoretic approach, of thematic analysis, allowing interpretive exploration of patterns, concepts and realities, will also be used. This method is appropriate for use due to the narrow field of enquiry within the interviews. Also, as the topics being covered are relatively understudied, an inductive methodology is more appropriate, which thematic analysis, and a phenomenological approach, both support.

Several steps will be made to analyse the data. Initially, research AB will ensure familiarisation with the data, gain through transcription and repeated reading of transcripts. Once familiarised with the data, initial coding of the data will be made, focusing on participant's experiences and views. Once all transcripts have been coded, codes will be charted and mapped to allow themes within the data to emerge. Codes will be linked, and from this, categorised into themes.

Appendix 5: MEDLINE search strategy

OVID Medline search strategy showing search development.

Lines 35, 44, 45, 46, 57, 58, 61, 62, 63, 64, 65, 107, 108, 109 and 110 are lines which identify major search concepts

Line 66 and 111are searches 1 and 2

Line 66 is the initial search which combined concepts of Proxy markers of malnutrition/nutrition assessment terms AND malnutrition terms AND older people AND cancer

Line 111 is the supplementary search 2 which combined specific named malnutrition screening tools AND older people AND cancer

1. ((proxy or surrogate) adj3 marker*).ti,ab,kw.
2. (marker* adj4 (nutrition* or malnutrition* or malnourish*)).ti,ab,kw.
3. marker*.ti.
4. Biomarkers/
5. biomarker*.ti,ab,kw.
6. Weight Loss/
7. body weight/ or weight loss/
8. weight loss.ti,ab,kw.
9. Body Composition/
10. Anthropometry/
11. Electric Impedance/
12. ((electric* or bioelectric*) adj3 impedance).ti,ab,kw.
13. (body composition or anthropometry).ti,ab,kw.
14. Feeding Behavior/
15. ((feed* or eat*) adj3 (behavior* or behaviour*)).ti,ab,kw.
16. APPETITE/
17. appetite*.ti,ab,kw.
18. Anorexia/
19. anorexi*.ti,ab,kw.
20. exp Energy Intake/
21. ((calorie* or energy) adj3 intake*).ti,ab,kw.

22. enteral nutrition/ or exp parenteral nutrition/

23. ((enteral or parenteral) adj3 nutrition).ti,ab,kw.

24. Inflammation/

25. inflammation*.ti,ab,kw.

26. exp body fat distribution/ or exp adiposity/ or exp body mass index/

27. (body adj3 fat).ti,ab,kw.

28. (BMI or body mass index).ti,ab,kw.

29. Skinfold Thickness/

30. skinfold thickness/ or waist-hip ratio/ or (skinfold adj2 thick*).ti,ab. or ((hip or waist) adj2 ratio).ti,ab.

31. "Body Weights and Measures"/

32. nutrition assessment/

33. Nutritional Status/

34. (nutrition* adj3 (assess* or state or status or screen*)).ti,ab,kw.

35. or/1-34 [proxy markers set]

36. PROTEIN-ENERGY MALNUTRITION/ or MALNUTRITION/

37. (nutrition* adj2 risk).ti,ab,kw.

38. (risk adj3 maln*).ti,ab,kw.

39. Nutritional Status/

40. (malnutrition* or malnourish* or mal-nutrition* or mal-nourish*).ti,ab,kw.

41. (undernutrition or undernourish*).ti,ab,kw.

42. (under?nutrition* or under?nourish*).ti,ab,kw.

43. protein energy malnutrition.ti,ab,kw.

44. or/36-43 [malnutrition set]

45. *MALNUTRITION/di [Diagnosis] [focused Malnutrition MESH term with diagnosis subheading]

46. (35 and 44) or 45 [(proxy markers AND malnutrition set] OR focused Malnutrition MESH with di subheading]

47. exp aged/ or exp "aged, 80 and over"/ or exp frail elderly/

48. exp Geriatrics/

49. (older or elderly or elder or elders or aging population or ageing population or nonagenarian* or octogenarian* or centenarian* or septuagenarian*).ti,ab.

50. Frailty/

51. (old* adj3 (people or person* or patient* or women or woman or men or man or adult* or individual* or population*)).ti,ab.

52. frail*.ti,ab.

53. (geriatric* or senior*).ti,ab.

54. Health Services for the Aged/

55. AGING/

56. (ageing or aging).ti,ab.

57. or/47-56 [older people set]

58. 46 and 57 [Combines malnutrition + proxy markers/focused malnutrition.di AND age limt]

59. exp NEOPLASMS/

60. (cancer$ or neoplas$ or tumor$ or tumour$ or malignan$ or carcinoma$ or metasta$ or oncolog$ or leukemi$ or leukaemi$ or lymphoma$ or myeloma$ or sarcoma$).mp.

61. 59 or 60 [cancer set]

62. 58 and 61 [combines proxy markers/malnutrition.di AND age limit AND cancer set]

63. (animals not humans).sh. [animal only studies]

64. 62 not 63 [excludes animal only studies]

65. (addresses or biography or case reports or comment or directory or editorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or practice guideline).pt. [publication types]

66. 64 not 65 [SEARCH 1 - excludes irrelevant publication types]

67. BAPEN.ti,ab,kw.

68. "British association for parenteral and enteral nutrition".ti,ab,kw.

69. BNST.ti,ab,kw.

70. "British Nutrition* Screening Tool".ti,ab,kw.

71. CNST.ti,ab,kw.

72. "Canadian Nutrition* Screening Tool".ti,ab,kw.

73. CONUT.ti,ab,kw.

74. "Controlling Nutrition* Status".ti,ab,kw.

75. ESPEN diagnostic criteria for malnutrition.ti,ab,kw.

76. (EDC and malnutrition).ti,ab,kw.

77. GNRI.ti,ab,kw.

78. Geriatric Nutrition* Risk Index.ti,ab,kw.

79. INSYST.ti,ab,kw.

80. Imperial Nutritional Screening System.ti,ab,kw.

81. "Imperial Nutrition and Metabolism".ti,ab,kw.

82. MST.ti,ab,kw.

83. Malnutrition screening tool.ti,ab,kw.

84. MSTC.ti,ab,kw.

85. Malnutrition Screening Tool for Cancer.ti,ab,kw.

86. Malnutrition Universal Screening Tool.ti,ab,kw.

87. (MUST and malnutrition).ti,ab,kw.

88. Nutrition* risk index.ti,ab,kw.

89. NRI.ti,ab,kw.

90. ((NRS-2002 or NRS) adj "2002").ti,ab,kw.

91. Nutrition* Risk Screening.ti,ab,kw.

92. NUFFE.ti,ab,kw.

93. Nutrition* form for the elderly.ti,ab,kw.

94. SGA.ti,ab,kw.

95. ((PG-SGA or PGSGA or PG) adj SGA).ti,ab,kw.

96. Subjective global assessment.ti,ab,kw.

97. Patient Generated Subjective Global Assessment.ti,ab,kw.

98. SNAQ.ti,ab,kw.

99. ((simplified or short) adj nutrition* assessment questionnaire).ti,ab,kw.

100. 3 Minute Nutrition* Screening.ti,ab,kw.

101. 3-MinNS.ti,ab,kw.

102. PNI.ti,ab,kw.

103. prognostic nutrition* index.ti,ab,kw.

104. MNA.ti,ab,kw.

105. mini nutrition* assessment.ti,ab,kw.

106. MNA-SF.ti,ab,kw.

107. or/67-106 [set of nutritional/malnutrition screening tools]

108. 57 and 61 and 107 [older people AND cancer AND specific malnutrition screening tools]

109. 108 not 62 [remove results of Search 1]

110. 109 not 63 [remove animal only studies]

111. 110 not 65 [remove irrelevant study types - SEARCH 2]

Appendix 6: MEDLINE search strategy for PENS review

Online Supplementary Material One – MEDLINE search strategy

MEDLINE Search

1. Nutrition Assessment/
2. ((malnutrition* or nutrition*) adj3 (screen* or risk*)).ti,ab.
3. Mass Screening/
4. (malnutrition* or nutrition*).ti,ab.
5. Nutritional Status/
6. *Malnutrition/di
7. Stress, Psychological/
8. overdiagnosis.ti,ab.
9. Anxiety/
10. false negative reactions/ or false positive reactions/ or (false adj (negative or positive)).ti,ab,kw.
11. exp Pain/
12. Unnecessary Procedures/
13. Psychological Trauma/
14. Patient Satisfaction/
15. "Patient Acceptance of Health Care"/
16. ((user* or people* or patient* or consumer* or adult* or subject* or caregiver* or care giver* or family or families or spouse* or relative* or carer*) adj4 (feeling* or emotion* or view* or experience* or perception* or perspective* or opinion* or accept* or satisfaction)).ti,ab,kw.
17. ((harm* or adverse*) adj4 screen*).ti,ab.
18. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 4 or 5
20. 3 and 19
21. 1 or 2 or 20
22. 18 and 21
23. 6 and 18
24. 22 or 23
25. limit 24 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")
26. limit 24 to ("all adult (19 plus years)" or "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)")
27. 25 not 26
28. 24 not 27
29. BAPEN.ti,ab,kw.
30. "British association for parenteral and enteral nutrition".ti,ab,kw.
31. BNST.ti,ab,kw.
32. "British Nutrition* Screening Tool".ti,ab,kw.
33. CNST.ti,ab,kw.
34. "Canadian Nutrition* Screening Tool".ti,ab,kw.
35. CONUT.ti,ab,kw.
36. "Controlling Nutrition* Status".ti,ab,kw.
37. ESPEN diagnostic criteria for malnutrition.ti,ab,kw.
38. (EDC and malnutrition).ti,ab,kw.
39. GNRI.ti,ab,kw.
40. Geriatric Nutrition* Risk Index.ti,ab,kw.
41. INSYST.ti,ab,kw.
42. Imperial Nutritional Screening System.ti,ab,kw.
43. "Imperial Nutrition and Metabolism".ti,ab,kw.

44. MST.ti,ab,kw.
45. Malnutrition screening tool.ti,ab,kw.
46. MSTC.ti,ab,kw.
47. Malnutrition Screening Tool for Cancer.ti,ab,kw.
48. Malnutrition Universal Screening Tool.ti,ab,kw.
49. (MUST and malnutrition).ti,ab,kw.
50. Nutrition* risk index.ti,ab,kw.
51. NRI.ti,ab,kw.
52. ((NRS-2002 or NRS) adj "2002").ti,ab,kw.
53. Nutrition* Risk Screening.ti,ab,kw.
54. NUFFE.ti,ab,kw.
55. Nutrition* form for the elderly.ti,ab,kw.
56. SGA.ti,ab,kw.
57. ((PG-SGA or PGSGA or PG) adj SGA).ti,ab,kw.
58. Subjective global assessment.ti,ab,kw.
59. Patient Generated Subjective Global Assessment.ti,ab,kw.
60. SNAQ.ti,ab,kw.
61. ((simplified or short) adj nutrition* assessment questionnaire).ti,ab,kw.
62. 3 Minute Nutrition* Screening.ti,ab,kw.
63. 3-MinNS.ti,ab,kw.
64. PNI.ti,ab,kw.
65. prognostic nutrition* index.ti,ab,kw.
66. MNA.ti,ab,kw.
67. mini nutrition* assessment.ti,ab,kw.
68. MNA-SF.ti,ab,kw.
69. or/29-68
70. 4 and 69
71. 18 and 70
72. limit 71 to "all child (0 to 18 years)"
73. limit 71 to "all adult (19 plus years)"
74. 72 not 73
75. 71 not 74
76. 28 or 75
77. (animals not humans).sh.
78. 76 not 77

Appendix 7: Charted matrix to allow comparison between studies

Online Supplementary Material Three

Charted matrix to allow comparison between studies

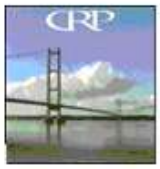
Theme	Sub-theme	Qualitative articles, quotes	Quantitative articles, results
Theme 1: Experience of screening	--	"That doesn't worry me on iota" (F7) (422) "Well it's quite simple. When you get to my age, you want things simple don't you?" (M1) (422) "Yes, it was very good that the topic [nutrition] was addressed" (TN09) (420) Participants were not clear on what was examined "Yes, what did she do?" (TN 09) (420) Did not feel the assessment was unpleasant or disturbing (420) "Oh my God, I want to avoid this! [refers to question about weight loss]. The hardest thing is when you lose weight when you actually don't want to" (P13, Woman) (555) When the form asked about functional decline and weight loss, it was difficult for some participants to answer honesty "I wish I could have selected "able to do little activity and spend most of the day in bed or chair". But to be honest, I have been lying in bed". (Participant 16, man).	99% of participants were happy to answer questions regarding their nutrition (415) 100% participants were happy to answer questions about their nutrition (416) Participants found the screening process acceptable (417) Questions were easy to understand (MST tool) (417) Screening may be confusing, or unnecessary (417) Participants were comfortable with screening process (418)
Theme 2: Understanding of malnutrition	Misunderstanding of malnutrition (not understood therefore	"Yes, I noticed it [weight loss], I'm better off, I'm was a bit too snug" (TN 01) (420) "I have lost a lot of weight, seven kilos, it was the end of my strength.	Requests for explanation of final score (meaning of low, medium

	following 'healthy eating' advice) (disbelief of results as following heathy eating advice)	It [weight loss] was bad and depressing" (TN 07) (420) Information gathered from magazines and family members: encouraged 'healthier' diets (420) "Then I drank actimel instead of water" (TN 08) (420) "Well I couldn't understand that. When I eat properly – I feel I eat properly – I couldn't understand why… then it showed that I was malnourished" (F5) (422) "I was initially kind of shocked that I scored… you know, I thought it would be higher" (421) "I sort of forgot it… I was a little bit upset when I got it" (421) "So in what way do you feel I… I'm not doing the right things?" (421) "Yeh well I eat loads of vegetables and so I found it ah… I am doing things right" (421) "Now I eat fruit instead of chocolate" (TN 01) (420) "I know what a good diet is" (419) "I'm 280 pounds. How can I be malnourished?" (419) Despite screening tool diagnosing risk of malnutrition, all rated nutritional health as 'fair' or 'good' (419) Trying to eat a healthy diet; maintaining a garden to eat fresh fruit and vegetables (419)	and high scores) were made (415)
	Risk perception: lack of understanding of risks and causes of malnutrition and nutrition leading to low risk perception, resulting in low prioritisation of results	"I feel I am not at risk, but I might be wrong" (421) "I'm 280 pounds. How can I be malnourished?" (419) "I felt that little applied to me probably because I had not properly completed the questionnaire" (421) "Well, it doesn't really bother me" (421) "I don't need it. No, we look after ourselves as far as cooking and eating is concerned. I think common sense has got a lot to do with it" (F6) (422) Cause of weight loss was not cancer, was due to dietary perceived positive dietary changes "I haven't lost weight because of the therapy, but	

		just because I eat less when I am alone" (TN 02) (420) "Now I eat fruit instead of chocolate" (TN 01) (420) "I no longer eat salmon or shrimp or seafood as they can have an effect on the cancer" (TN 08) (420) "I drank actimel instead of water" (TN 08) (420) "I will never buy a frozen dinner. There's no way I'm going to touch that because of the chemicals" (421) "Well because of the issues I have with my son and his children, I didn't really take an awful lot of notice of it I'm afraid. I'm sorry, I should have but I didn't" (F4) (422)	
	Understanding role of screening (low perception of risk, therefore advice is unwanted)	"That was not relevant for me" (TN10) (420) "I think weight loss is related to everything, food and illness" (TN 06) (420) "The nurses, they have to ask, that's what you have to do with all the patients, but that was not relevant for me now" (TN 10) (420) "Well they can't do much. It's me getting old, tired and worried and well, you know (F2) (422) "I didn't follow it. No, I didn't actually – she [practice nurse] told me what cereal to take in the morning but I tried it – one plateful but I couldn't eat it" (F4) (422)	Screening seen as unnecessary (417) Participants understood the need and importance of nutritional screening (418)
Theme 3: Barriers to, and opportunities for change – many feel	Rationalising current dietary intake Lack of readiness to change (lifetime habits) (barriers to change) Advice does not apply as they are following mainstream guidelines	"That's what you do with all the patients… but that was not relevant for me" (TN10) (420) "It's not a continual practice or we don't do it for any particular reason other than we're in a hurry or you've had a late breakfast or we've been out for breakfast" (421) "That was not relevant for me" (TN10) (420) Patients felt comfortable continuing to do things their own way "We saw a dietitian about two or three times. As I said, the advice she gave us, well-meaning, but I didn't consider it all that helpful (M6) (422) "I've never had soy milk in my life, so I wouldn't know what it tastes like.	

		And if I don't know, I wouldn't buy it" (421) "You have to have fat on meat to cook it anyway. But see, there is my upbringing" (421) "I don't feel I'm as much at risk as… as the community at large. And that's what bothers me are the people out there. They're far more at risk I feel" (421) "Sometimes when you're working, you're rushing all the time" (421) "The recommendations were good for the average person, but like I said, I believe that I eat and watch my diet quite well" (421) "I'm 280 pounds. How can I be malnourished?" (421) Participants saw screening results as an assessment of how well they were doing the right things (421) "Yes, the biggest problem is my appetite. You know, I just don't feel like eating" (421) "Well they can't do much. It's me getting old, tired and worried and well, you know (F2) (422) "I am cutting down a little on the amount of red meat we eat but I decided that by myself" (F6) (422)	
	Opportunities for learning	"Yes, it was very good that the topic [nutrition] was addressed" (TN09) (420) "It may be beneficial to all old people I suppose to be quite honest and if things are required after that well it'd most probably be a good thing you know (M2) (422) "It's quite informative, very good" (F5) (422) "It's a matter of… something we should know about and do something about" (421) "I count on the medical profession to let me know if they see that there is something wrong. If my weight drops or whatever, then I hope they will ring bells and say "Hey!" (421) "That's very important, to try new things. Things that maybe you didn't grow up with or you just aren't used to" (419)	

Appendix 8: Trans-Humber Consumer Research Panel feedback form



Trans-Humber Consumer Research Panel

Promoting public and professional partnership in medical research since December 2004

c/o Therapies Centre,
Hull Royal Infirmary,
Anlaby Road,
Hull.
HU3 2JZ
Tel: 01482 605291

Alex Bullock,
Clinical Research Fellow (Nutrition)
Hull York Medical School
Allam Medical Building
The University of Hull
Hull,
HU6 7RX

13th July 2019

Re: DEVELOPMENT, REFINEMENT AND ACCEPTABILITY OF A SINGLE CLINICAL SCREENING TOOL TO DETECT MALNUTRITION, SARCOPENIA AND CACHEXIA IN OLDER ADULTS WITH CANCER

Dear Alex,

Firstly I would like to thank you very much for sending the documentation for the above study to our Consumer Research Panel for review. The panel felt it was a valuable study to inform patient care, and could see the potential for the tool that you plan to develop.

The panel were happy that their suggested amendments have been incorporated into the study documentation and that you have produced documents which are in Plain English and are unambiguous.

We wish you every success in your research.

Yours sincerely,

Angela Green

(Chair Trans Humber Consumer Research Panel)

Appendix 9: Data collection form

Identification Number:		**Consent to interview:** Yes / No
Age:	**(yrs)**	
Diagnosis:	**General:** Breast Lung Prostate Colorectal H&N UGI **Specific:** **TNM:**	
Blood results	Albumin: _____ g/l, Date: ___ / ___ / _____, Days since recorded: _____ Hb: _____ g/l, Date: ___ / ___ / _____, Days since recorded: _____ CRP: _____ mg/l, Date: ___ / ___ / _____, Days since recorded: _____ Lymphocyte count: _____ µ/l, Date: ___ / ___ / _____, Days since recorded: _____	
PMH	MI / Congestive heart failure / peripheral vascular disease / TIA or Stroke / Dementia / COPD / Connective tissue disease e.g. rheumatoid arthritis / Peptic ulcer disease / Liver disease / Diabetes / Hemiplegia / Moderate or Severe CKD / Solid tumour / Leukaemia / Lymphoma / AIDS	
SHx	NOK / partner / Family members (not partner) / Carer / Other Additional details:	
SHx	Retired / Full time employed / Part time employed / Other	
SHx	Non-smoker / Ex-smoker / Current smoker	
Rockwood	Very fit / Well / Managing / Vulnerable / Mildly frail / Moderately frail / Severely frail / Very severely frail / Terminally ill	
Height: (cm)		**BIA:** **Weight, kg: _____** **Body fat %: _____** **Total body water %: _____** **Muscle mass, kg: _____** **Bone mass, kg: _____**
Mid Arm Circumference: (cm)		
Hand-grip (kg) dominant hand 1st test: 2nd test: 3rd test:		**Chair-stand test (reps, secs) (30 seconds, wrist crossed, reps)**
		Timed-up-and-go test (secs) (seated, walk 3m, turn, walk, sit)
Weight history (3, 6, 12 months) (kg, %)		**Visual assessment:** **Temples**: Hollowing / slight depression / defined **Clavicles**: Protruding / slight protrusion / not visible **Emaciated**: Yes / No
Type of PO intake: Normal (solids) / soft diet / liquids only / minimal / NBM		
Regularly uses: ONS / EN / PN / NIL		
Eating approximately: all / 75% / 50% / 25% / < 25% **of my normal meals**		
Requirement for assistance with eating: No / some / complete		
Food preparation: Self / NOK / Family member / Other:		
Food shopping: Self / NOK / Family member / Other:		
Fluid intake per day: (non-alcohol) _____mls or no' of cups/mugs per day: _____		
GI problems:		

Oral: pain / dryness / difficulty swallowing **Diarrhoea:** Yes / No **Nausea or vomiting:** Yes / No **Constipation:** Yes / No
(SARC) **How much difficulty do you have lifting or carrying 10lb?** (4.5 bags of flour) N*o difficulty* / some difficulty / *a lot or unable to do*
(SARC) **How much difficulty do you have walking across a room, and do you need help to do this?** N*o difficulty* / some difficulty / a lot of difficulty (use of aids, or unable to do without help)
(SARC) **How much difficulty do you have transferring from a chair or bed, and do you need aids or help to do this?** N*o difficulty* / some difficulty / a lot of difficulty (use of aids, or unable to do without help)
(SARC) **How much difficulty do you have climbing (a flight of) 10 steps?** N*o difficulty* / some difficulty / *a lot or unable to do*
(SARC) **How many times have you fallen in the last year?** No falls in the past year / 1 to 3 falls in the last year / four or more falls in the past year
(CACH) **Do you have to put more effort into climbing the stairs?** Not at all / A little / Quite a bit / Very much
(CACH) **Have you felt tired after walking approximately 500m?** Not at all / A little / Quite a bit / Very much
(CACH) **My appetite is…** Very good / Good / Average / Poor / Very poor
Question regarding how much you need to eat in order to feel full: (CACH) **When I eat I feel full**… hardly ever / after eating **most** of a meal / **half** a meal / **third** of a meal / only a **few mouthfuls**
Next questions; in the last **WEEK**
(CACH) Do you need to stay in bed or a chair during the day? Not at all / A little / Quite a bit / Very much
(CACH) Were you limited in doing your work or daily activities: Not at all / A little / Quite a bit / Very much
(CACH) Were you limited in perusing your hobbies or other leisure activities? Not at all / A little / Quite a bit / Very much
(CACH) Have you had pain? Not at all / A little / Quite a bit / Very much
(CACH) Do you need to rest? Not at all / A little / Quite a bit / Very much
(CACH) Have you felt weak? Not at all / A little / Quite a bit / Very much
(CACH) Did pain interfere with your daily activities? Not at all / A little / Quite a bit / Very much
(CACH) Have you had difficulty concentrating on things e.g. watching TV or reading? Not at all / A little / Quite a bit / Very much
(CACH) Has your physical condition or medical treatment interfered with your family life? Not at all / A little / Quite a bit / Very much
(CACH) How do you rate your overall health during the past week? Excellent / Fine / Poor / Very poor
(CACH) How do you rate your quality of life over the past week? Excellent / Fine / Poor / Very poor

Appendix 10: Original plan for quantitative data analysis

Regression analysis

Regression analysis enables the exploration of the relationships between outcomes of interest ('dependent variables') and predictors of interest ('independent variables'). For this study, the primary dependent variables were the presence (or absence) of the three conditions of interest (malnutrition, sarcopenia, and cachexia). Secondary outcomes were the patient outcome measures, including survival. The independent variables are the markers of the three conditions, answers to the screening questions (e.g., body weight loss, biomarkers, as outlined in appendix 1.0), and available demographic data. For continuous dependant variables (e.g., length of hospital stay), linear regression will be used. Where the dependant variables are binary (e.g., diagnosis of sarcopenia) or categorical (e.g., category/severity of cachexia), logistic regression models will be employed. Univariate regression models to investigate the relationship between each independent variable and each dependent variable will be used. The results from these analyses (i.e., effect sizes and tests of statistical significance), along with the results of a systematic review investigating the relationship between markers of malnutrition and patient outcomes, other relevant literature, and the results of the qualitative interviews, will be used to select independent variables for inclusion in multivariate analyses. On univariate analysis, a p-value of <0.20 will mark inclusion of a variable for multivariate analysis. Multivariate models allow for confounding effects to be controlled for. A stepwise approach, with inclusion criteria being $p<0.05$ on multivariate analysis, or variables which have been identified as relevant during literature review, or participant interviews and have sufficient justification for inclusion will be used to develop the final screening tool.

Survival analysis

Kaplan-Meier curves, used to manage time-to-event data (1), are planned to examine the relationship between the presence or absence of a diagnosis of malnutrition, sarcopenia or cachexia and participant survival outcomes. Depending on data quantity, additional curves, for independent markers, such as body mass index (BMI) or percentage weight loss, could be dichotomised to examine their relationship with patient outcomes.

Diagnostic test evaluation

As many of the markers of the conditions being investigated, markers for malnutrition in particular, have either disputed or arbitrary thresholds. Receiver Operating Characteristic (ROC) curves could be used to select optimal thresholds for markers based upon their sensitivity and specificity. ROC curve analysis could be used, for markers such as percentage weight loss, BMI, hand-grip strength, to determine appropriate thresholds for predicting outcomes.

Appendix 11: Clinician and patient participant interview sampling methods for screening tool refinement

The sample size for both recruitment of clinician and patient participants, was empirical. Estimated sample sizes of five to eight clinician participants, and eight to 15 patient participants were estimated based upon expected recruitment rates of clinicians (a rate limiting step). The aim of this sample size would have been to gain sufficient feedback regarding the acceptability and utility of the tool in clinical practice, to allow development of the tool, and initial testing of clinical feasibility. Purposive sampling, to select respondents most likely to provide valuable feedback, was planned.

Planned purposive sampling frame for screening tool refinement

Eligibility criteria planned for Stage Three interview sampling:

Patient participants

- Age (70 – 79, and >80)
- Medical diagnosis

	H&N, UGI	**Breast, Prostate**	**Lung, Colorectal**
70 – 79 years			
>80 years			

Clinician participants

- Location of work
- Role

	Dietitian	**Registered nurse**	**Auxiliary nurse**
Inpatients			
Outpatients			

Appendix 12: Interview topic guide

Exploring patient views, experiences and understanding of assessments for malnutrition, sarcopenia and cachexia (MSC)

Aims and objectives

The central aim of this interview is to explore patient's views, experiences and understanding regarding assessments for malnutrition, sarcopenia and cachexia (MSC) following a cancer diagnosis

Main objectives to explore:

- The experiences of patient's regarding assessments for MSC
- The views of patient's concerning assessments for MSC
- Patient's understanding of assessments for MSC

Introduction

Aim: To introduce the research and set the context for the proceeding discussion.

- Introduce self and Hull York Medical School
- Introduce the study: who it is for and what it is about
- Talk through key points:
    - Purpose and length of interview
    - Any expenses refunded for travel
    - Voluntary nature of participation and right to withdraw
    - Recording of interview
- Confidentiality and how findings will be reported
- Any questions

Background and experience of cancer journey

Aim: To explore the experiences of cancer journey

"I have read your medical notes and know about your diagnosis and treatment so far, but I wonder if you could tell me about your experience in own words?"

- Elicit interactions with healthcare staff
    - Outpatient specialist, inpatient teams, clinical nurse specialists, allied healthcare professionals

Experiences of assessment for MSC

Aim: To explore the experiences of patient's regarding assessment for MSC

- For BOTH **nutrition** AND **activity levels or function**
    - "During your treatment / since your diagnosis, has anyone asked you about nutrition / activity or function"
    - If yes;
        - What were you asked?

        - Who asked you this?
        - How were you asked?
        - Why do you think you were asked?
    - If no; progress to next question

Views of assessment for MSC

Aim: To explore the views of patient's concerning assessment for MSC

- When asked about MSC:
    - How did you feel about being asked?
    - What was good?
    - What was bad?
    - What could be changed (if anything)?
        - Prompts: company, timing of assessment, who to conduct assessment, sense checking of questions

Patient's understanding regarding MSC

Aim: To explore patient's understanding of assessments for MSC

- "Has anyone mentioned to you…"
    - Malnutrition (problems with your eating)?
    - Sarcopenia (problems with muscle wasting or weakness)?
    - Cachexia (weight loss caused by cancer)?
- "What do you understand by these terms?"

"Do you think problems with MSC affect your health?"

- Physical
- Mental
- Social

Is there anything else you would like to mention?

Conclusion

- Thank participant for time
- Remind about confidentiality and anonymity
- Provide refund of travel expenses

Appendix 13: Planned purposive sampling frames

Eligibility criteria planned for use with purposive sampling

- Age (70- 80, >80)
- Diagnosis of malnutrition, sarcopenia, or cachexia: presence and absence
- Diagnosis of cancer; grouped by expected prevalence of malnutrition and/or cachexia, groups: H&N & UGI, Breast & Prostate, Lung & Colorectal
- Presence / absence of a carer

	Presence malnutrition	**Absence malnutrition**	**Presence sarcopenia**	**Absence sarcopenia**	**Presence cachexia**	**Absence cachexia**
H&N, UGI						
Breast, Prostate						
Lung, Colorectal						

	Carer	**Self-care**
70 – 79 years		
>80 years		

Appendix 14: HYMS ethics approval

Hull York Medical School
Hull
University of Hull
Hull, HU6 7RX, UK
York
University of York
York, YO10 5DD, UK
T 0870 1245500
info@hyms.ac.uk
www.hyms.ac.uk

24 July 2019

Miss Alex Bullock
Clinical Research Fellow (Nutrition)
Hull York Medical School

Dear Alex

19 34 Development, refinement and acceptability of a single clinical screening tool to detect malnutrition, sarcopenia and cachexia in older adults with cancer

I have reviewed this study on behalf of HYMS Ethical Committee.

I am pleased to inform you that I do not have any HYMS specific ethical concerns and am happy to give HYMS Ethics approval.

Please forward a copy of HRA approval once obtained for our HYMS EC file.

Kind regards

Yours sincerely

Professor Thozhukat Sathyapalan
Chair
HYMS Ethics Committee

Appendix 15: University of Hull sponsorship

UNIVERSITY OF HULL

Dr David Richards
Pro-Vice-Chancellor
(Research, Enterprise and Marketing)
University of Hull
Hull, HU6 7RX
United Kingdom
T: +44 (0)1482 466732 | w: www.hull.ac.uk
E: David.Richards@hull.ac.uk

1st August 2019

Alex Bullock
(HYMS, FHS)

Dear Alex

PI: Alex Bullock (HYMS/FHS)
REF: RS123

I am writing to confirm that the University of Hull has agreed to act as sponsor, subject to approval being granted in accordance with the Department of Health Research Governance Framework for the project "Optimisation of the detection and assessment of malnutrition, sarcopenia and cachexia in older cancer patients".

Yours sincerely

Dr David Richards
Pro-Vice-Chancellor (Research & Enterprise)
(Chair of University Research and Enterprise Committee)

cc Dean

Appendix 16: Research ethics committee approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Alex Bullock
Clinical Research Fellow (nutrition)
University of Hull
Hull York Medical School
Allam Medical Building
University of Hull
HU67RX

Email: hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

29 November 2019

Dear Miss Bullock

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Development, refinement and acceptability of a single clinical screening tool to detect Malnutrition, Sarcopenia and Cachexia in Older Adults with Cancer**
IRAS project ID:	**260177**
Protocol number:	**Version 2.5**
REC reference:	**19/LO/1479**
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.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

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 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) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

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 standard conditions 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.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **260177**. Please quote this on all correspondence.

Yours sincerely,
Rachel Katzenellenbogen
Approvals Specialist

Email: nrescommittee.london-central@nhs.net

Copy to: Dr Andrew Taylor, University of Hull

Appendix 17: HUTH R&D capability and capacity confirmation

Alex Bullock

From: Hunn, Louise <Louise.Hunn@hey.nhs.uk>
Sent: 07 January 2020 10:32
To: Alex Bullock
Subject: R2412 Confirmation of Capability and Capacity

Dear Ms Bullock

Confirmation of Capacity and Capability at Hull University Hospitals Teaching NHS Trust

(Please retain a copy of this email as this confirms NHS permission for this site)

IRAS: 260177
LOCAL ref: R2412
EDGE ID: 126553
REC ref: 19/LO/1479

Full Study Title: Development Refinement and Acceptability of a Single Clinical Screening Tool to Detect Malnutrition Sarcopenia and Cachexia in Older Adults with Cancer

PI: Ms A Bullock
Academic Supervisors: Prof M Johnson
Sponsor: University of Hull

This email confirms that Hull and East Yorkshire Hospitals NHS Trust has the capacity and capability to deliver the above referenced study.

It is noted that all internal and regulatory approvals are in place.

If you do not currently hold the appropriate contract of employment with the Trust (Full or Honorary) please inform me prior to commencing your study at this site

Please inform me of the actual date the research activity commences

You will shortly receive an email requesting you to set up your account on the EDGE system

The study is on the EDGE database www.edge.nhs.uk and can be found using the R&D reference, IRAS number, EDGE ref or the study title all shown above

You will need to ensure the study is updated on EDGE with the following;

- All patient screening/recruitment data. Via the patient tab

If you need any further support from R&D please do not hesitate to contact me.

With best wishes for a successful study

Kind regards
Lou

Louise Hunn
Research Facilitator RDU 1

1

NHS
Hull University Teaching Hospitals
NHS Trust

Appendix 18: Patient Information Sheet

Developing a single screening tool to detect eating and muscle problems and weight loss in older adults with cancer

A large-print version of this sheet is available on request

Invitation to take part in a research study

We invite you to take part in a research study. This sheet is to help you to decide if you would like to take part. It explains why the research is being done, what you will be asked to do, and why we are inviting you to take part. Please take your time to read the following information; you might want to discuss it with your friends or family. Alternatively the research team can explain anything that is not clear to you. The study is organised and run by the Yorkshire Cancer Research TRANSFORM Group at the University of Hull. This research is part of a PhD qualification for researcher Alex Bullock.

What is the study about?

We want to find a way to check older people with cancer for eating problems, weak muscles or cancer-related weight loss that is acceptable for patients and the clinical team. We know that problems with their eating, weight or muscle health may affect quality of life and use of cancer treatments. During this study we will produce a short test tool to find out which, if any, of these problems patients have. We will also find out if people and their clinicians find this tool useful, practical or acceptable.

What will happen to me if I take part?

If you agree to take part, you will be asked to sign a consent form. A member of the research team will arrange a convenient time for you to complete the study measures. This could be before or after your clinic appointment at the Queens Oncology Centre, or at another convenient time. If you are an inpatient this can be at a time that suits you on your ward. The researcher will ask some questions about your medical condition, eating habits, your weight, and active you are. You will also be asked to do a short walking test, a sit to stand test, and have physical measures of your muscle strength taken.

You can also take part in an interview at a time and place of your preference; at your home, the Queens Oncology Centre or the University of Hull. The interview will take between 30 minutes and an hour and be audio recorded by the researcher so that your views are documented accurately. You can still take part in the other study measures if you do not want to be interviewed. In the unlikely event that you tell us something that gives us cause for concern, this will only be disclosed with your permission, or except as required by law. Not every participant willing to be interviewed will be needed for this part of the study.

Do I have to take part?

No, it is up to you to decide. You do not have to give a reason if you decide not to take part in the study and this will not affect your clinical care in any way. If you decide to take part, but change your mind you are free to withdraw at any time without giving a reason.

What are the positives of taking part?

Although it is unlikely that there will be a direct benefit to you in the short term, your taking part could directly benefit other people with cancer in the future.

Are there any negatives to be considered if I decide to participate?

We do not expect you to experience any disadvantages from taking part in this study, other than taking your time. However, it is possible you may find some of the questions may make you think about sensitive issues relating to your cancer. If you have any concerns, you will be able to speak about them with the researcher or the team treating you. Also, you may find that some of the study measures are too strenuous for you. If this is the case, you will be asked not to do them. The researcher can provide you with the contact details of the support services and health professionals available to you.

Will taking part in this study cost me anything, and will I be paid?

Taking part in this study will not cost you anything. We will be able to pay your travel expenses, at a cost of 28p per mile for car journeys plus parking costs, or the cost of public transport, if you wish to take part in the study outside of a usual clinic appointment time.

Will my involvement be confidential?

The University of Hull is the Sponsor for this study. We will use information from you and your medical records to carry out this study. We will act as the data controller, that is, we are responsible for looking after your information and using it properly. The University of Hull will keep identifiable information about you for up to 6 months after the study has finished. One of the tests (for cancer-related weight loss) is a computer based test held on a secure site in Barcelona University in Spain. Pseudonymous data (your personal details will be removed, and replaced with a code so you can only be identified by members of the research team) will be entered and the test results calculated by the computer. No other data will leave the UK. Your right 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 by contacting Mr Luke Thompson, Information Compliance Officer, University of Hull,

l.thompson3@hull.ac.uk or you can read the University of Hull Research Participant Privacy Notice supplement.

We will use your name and contact details for the purpose of contacting you for study visits or inform you of the study results. Only authorised researchers at the University of Hull will have access to information that identifies you. 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.

Individuals from the University of Hull and regulatory organisations may look at your medical and research records to check accuracy of the research study. Hull University Teaching Hospital NHS Trust oversees the quality of research conducted within the Trust and may 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 your care.

Anonymous information collected for the study may be provided to authorised researchers and used in other research studies in this or other organisations such as universities, NHS organisations or companies involved in health and care research in this country or abroad. For example, anonymous information collected for the cancer weight loss test may be used by the researchers in Spain who run the computer test calculation in other studies. Your information will only be used by organisations and researchers to conduct research in accordance with the *UK Policy Framework for Health and Social Care Research*. The information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of healthcare research, and cannot be used to contact you or to affect your care. Please indicate on the consent form if you are happy for this to occur.

How do I make a complaint?

If you have any concerns about the way the study was carried out, or any other aspects of your care, and feel unable to raise this directly with the research team, you may contact: Danielle Smith, Research Governance and Policy Manager, University of Hull. Tel: 01482 466962 or d.g.Smith@hull.ac.uk. You may also contact the Hull University Teaching Hospitals Patients Advice and Liaison Service (PALS). Tel: 01482 623065 or pals.mailbox@hey.nhs.uk

What will happen to the results of the research study?

The results of this study will help us develop a simple way to check patients aged over 70 with cancer for poor diet, cancer-related muscle loss and age-related muscle loss, and will also help us learn how people feel about being checked for these problems. We will also present the results in medical journals and at conferences and public engagement events. If you would like to receive a summary of the study's findings, please tick the box on the consent form.

Approvals

The study has been reviewed and approved by the Hull York Medical School Research Ethics Committee, the NHS Ethics Research Committee and Health Research Authority. The University of Hull has appropriate insurance and indemnity schemes in place.

Who can I contact for further information?

If you have any further questions about this research study, please do not hesitate to contact the Study Investigator: Alex Bullock, Tel: 01482 462217

alex.bullock@hyms.ac.uk

Thank you for taking the time to read this information sheet.

Appendix 19: Consent form

Patient Participant Informed Consent Form for 'Step One'

Developing a single screening tool to detect eating and muscle problems and weight loss in older adults with cancer

Name of lead researcher: Alex Bullock **Please initial the boxes**

1. I confirm that I have understood the information sheet dated 03.07.2019 (version 1.3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that study data will be collected by the researcher. ☐
4. I agree that anonymised and pseudonymised data can be used by authorised researchers working on similar studies: (please circle) Yes No ☐
5. I agree that relevant sections of my medical notes and data collected during this study may be looked at by responsible individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. ☐
6. I agree that my lead clinician can be contacted to inform them of my involvement in the study, and if any results of the study give cause for concern. ☐
7. I agree to take part in the interview for the above study. ☐
8. I agree that anonymous quotations from my interview can be used in presentations or publications arising from this project. ☐
9. I agree to take part in the above study. ☐

I would like a copy of the summary results of the study Yes No

Patient Signature……. Print Name……..
Date:……..

Investigator Signature……. Print Name……..
Date:……

Witness Signature……. Print Name……..
Date:……

Appendix 20: IRAS amendment tool

Amendment Tool

v1.2 11 Jun 2020

For office use
QC: No

Section 1: Project information

Short project title*:	MSC TRANSFORM
IRAS project ID* (or REC reference if no IRAS project ID is available):	260177
Sponsor amendment reference number*:	RS123
Sponsor amendment date* (enter as DD/MM/YY):	11 September 2020
Summary of amendment including justification*:	Study amendments due to COVID 19. All amendments related to minimising risk to research participants and researchers involved in the study. Key amendments include: location of assessments, requirement for personal protective equipment (PPE), following of local NHS Trust guidance for PPE and contact with patient participants. Changes to study protocol, participant information sheets and participant consent forms are included. Only change in information to be collected is the COVID-19 status of participants, as, to ensure safety, only participants with a negative COVID swab/without COVID symptoms will be approached for involvement. COVID status of participants to be recorded.

Project type:	◉ Specific study ○ Research tissue bank ○ Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	◉ Yes	○ No		
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable?:	◉ NHS/HSC REC ○ Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a modified amendment?	○ Yes	◉ No		
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	◉	○	○	○
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	○ Yes	◉ No		
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	○ Yes	◉ No		
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	○ Yes	◉ No		
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	○ Yes	◉ No		
Did the study involve adults lacking capacity OR does the amendment introduce this?:	○ Yes	◉ No		
Did the study involve access to confidential patient information without consent OR does the amendment introduce this?:	○ Yes	◉ No		
Did the study involve prisoners OR does the amendment introduce this?:	○ Yes	◉ No		
Did the study involve NHS/HSC organisations prior to this amendment?:	◉ Yes	○ No		
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	○ Yes	◉ No		
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	◉	○	○	○
Which nations had participating NHS/HSC organisations prior to this amendment?	☑	☐	☐	☐
Which nations will have participating NHS/HSC organisations after this amendment?	☑	☐	☐	☐

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the amendment tool as three separate changes. A list of all possible changes is available on the "Glossary of Changes" tab. To add another change, tick the "Add another change" box.

Change 1	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Inclusion/exclusion criteria - Minor change unlikely to affect safety or scientific value of study

Appendix 21: HUTH R&D confirmation of restart capacity and capability – October 2020

Alex Bullock

From: Hunn, Louise <Louise.Hunn@hey.nhs.uk>
Sent: 06 October 2020 16:06
To: Alex Bullock
Subject: R2412 Confirmation of RESTART C&C

Dear Alex,

Confirmation of RESTART Capacity and Capability at Hull University Teaching Hospitals NHS Trust. – please retain a copy of this email in the study file for future reference

RE: R2412 / IRAS: 260177

Full Study Title: Development, refinement and acceptability of a single clinical screening tool to detect Malnutrition, Sarcopenia and Cachexia in Older Adults with Cancer

This email confirms that Hull University Teaching Hospitals NHS Trust has Continuing Capacity and Capability (C&C) to deliver the above referenced study following the temporary suspension of recruitment due to the COVID-19 Pandemic

This confirmation of C&C is issued on the basis of information supplied by you as PI as part of the Trust's research restart framework, specifically:

- That the answers provided in the restart checklist are a true and accurate reflection of the position at the time of making the restart request to R&D
- That the restart of research activities will not be detrimental to the Trusts delivery of Urgent Public Health Research (nationally or locally mandated). A future request for flexibility to deliver this work should be acknowledged.
- That you have (on file and available upon request) the evidence as requested in the restart checklist notes,
- That you have received confirmation of capacity to restart from all relevant support services and service managers
- That you have undertaken (and have on file and available on request) all relevant risk assessments and mitigation plans
- That you have taken all necessary COVID-19 safety precautions in line with national and local Trust policies.

Please note: Confirmation of sponsor green light is required before any study activity can recommence at this site.

You are reminded of the need for the study team to update all patient screening and recruitment data on EDGE (weekly as a minimum please).

Kind regards

Lou

Louise Hunn
Research Facilitator & RDU 1 Delivery Lead

Hull University Teaching Hospitals NHS Trust
Research & Development
Floor 2, Daisy Building,
Castle Hill Hospital

NHS
Hull University Teaching Hospitals
NHS Trust

1

Appendix 22: HUTH correspondance study pause

Alex Bullock

From: Research Governance <researchgovernance@hull.ac.uk>
Sent: 19 November 2020 16:01
Subject: HUTH R&D Strategy Update: COVID-19

Dear colleagues,

In light of the current spike in COVID-19 cases within Hull, Hull University Teaching Hospitals NHS Trust (HUTH) has taken the decision to free up capacity to support urgent public health priorities.

Why have I been contacted?

This email has been sent to you as you have been identified within the University's sponsorship records as leading on, or participating in a research study involving HUTH – either with an identified HUTH R&D lead or HUTH site identified within your initial IRAS application.

If your study has completed or you do not believe you should be in receipt of this email, please contact researchgovernance@hull.ac.uk to update our records.

What is the HUTH strategy?

The three national levels of prioritisation set out within the Restart Framework still apply, with some further prioritisation within Level 1 to identify the highest priority COVID-19 UPH studies:

- **Level 1a (Top Priority)** - COVID-19 UPH vaccine and prophylactic studies (as prioritised by the Vaccines Task Force and agreed by Jonathan Van-Tam, deputy CMO) and platform therapeutics trials (currently RECOVERY/RECOVERY +; PRINCIPLE; REMAP CAP).
- **Level 1b** - Other COVID-19 UPH studies
- **Level 2** - Studies where the research protocol includes an urgent treatment or intervention without which patients could come to harm. These might be studies that provide access to potentially life preserving or life-extending treatment not otherwise available to the patient.
- **Level 3** - All other studies (including COVID-19 studies not in Level 1a or 1b).

If you are unsure which level applies to your study please contact researchgovernance@hull.ac.uk.

Full details of the HUTH strategy are available on request but, in summary:

- Level 3 patients should not be asked to attend hospital solely for research visits. Only patients involved in COVID-19 studies (levels 1a and 1b) or who require urgent treatment or intervention to prevent harm (level 2) may attend the hospital for research purposes.
- Level 3 studies should be paused unless they can be justified and they do not utilise resource which could be used for a level 1a or 1b (COVID-19) study.
- Each study will need to be considered on a case by case basis – studies which do not pose a COVID-19 risk to patents and which do not detract resources from the NHS / Level 1a and 1b research may still proceed.

How does this affect me?

Level 2 studies:

- Please continue with your study but consider whether any further amendments are required to prevent any unnecessary patient visits to HUTH.

Level 3 studies:

- If you believe that, based on the information above, you may be able to continue with your existing study / application for sponsorship at this time, please contact the R&D Manager at HUTH, James Illingworth (James.Illingworth@hey.nhs.uk) to discuss.
- If your study is an existing level 3 study, and you have been given permission to proceed without introducing any mitigations then no further action is required.
- If your study is an existing level 3 study and you are required to pause your study for a duration which will extend the study beyond the specified end date; or if you will need to amend your study protocol to include mitigations, you will be required to submit an amendment to the HRA. A new amendment tool is available on IRAS, and guidance on the University's internal process for submitting amendments is available on SharePoint. Further guidance is available from researchgovernance@hull.ac.uk.
- If you are in the process of submitting an application for Sponsorship (at any stage) then you may wish to consider whether your application / protocol may be amended to either:
  - Push back the start date
  - Introduce mitigations to enable your study to proceed

  Your application may still be submitted and processed but Research Governance and Policy Manager will work with you update the HRA of any potential delays in commencing your study / or to ensure any amendments are appropriately considered.

  Please contact researchgovernance@hull.ac.uk for to discuss further, if necessary.

Please note that where external funding awards are secured to support University sponsored work with UHTH, you will be required to consider whether any funding extensions are required and the expectations of the funding bodies at this time.

Please contact researchgovernance@hull.ac.uk if you have any queries or concerns or would like to discuss the detail of this email further.

Please also note that the research governance inbox is not monitored on Friday. Any queries will be responded to as soon as possible in the following week.

Kind regards

Katie

UNIVERSITY OF HULL

Katie Skilton| Research Governance and Policy Manager | Research and Enterprise
University of Hull
Hull, HU6 7RX, UK
www.hull.ac.uk
k.skilton@hull.ac.uk | 01482 466308

@UniOfHull /UniversityOfHull universityofhull

Appendix 23: HUTH R&D confirmation of restart capacity and capability – April 2021

Alex Bullock

From: Hunn, Louise <Louise.Hunn@hey.nhs.uk>
Sent: 22 April 2021 09:53
To: Alex Bullock
Subject: R2412 Confirmation of Restart April 2021

Dear Alex

Confirmation of RESTART Capacity and Capability at Hull University Teaching Hospitals NHS Trust. – please retain a copy of this email in the study file for future reference

RE: R2412 / IRAS: 260177

Full Study Title: MSC TRANSFORM – Development, Refinement and Acceptability of a Single Clinical Screening Tool to Detect Malnutrition, Sarcopenia and Cachexia in Older Adults with Cancer

This email confirms that Hull University Teaching Hospitals NHS Trust has Continuing Capacity and Capability (C&C) to deliver the above referenced study following the temporary suspension of recruitment due to the COVID-19 Pandemic

This confirmation of C&C is issued on the basis of information supplied by you as PI as part of the Trust's research restart framework, specifically:

- That the answers provided in the restart checklist are a true and accurate reflection of the position at the time of making the restart request to R&D
- That the restart of research activities will not be detrimental to the Trusts delivery of Urgent Public Health Research (nationally or locally mandated). A future request for flexibility to deliver this work should be acknowledged.
- That you have (on file and available upon request) the evidence as requested in the restart checklist notes,
- That you have received confirmation of capacity to restart from all relevant support services and service managers
- That you have undertaken (and have on file and available on request) all relevant risk assessments and mitigation plans
- That you have taken all necessary COVID-19 safety precautions in line with national and local Trust policies.

Please note: Confirmation of sponsor green light is required before any study activity can recommence at this site. – **This email Constitutes Sponsor Green Light to proceed**

You are reminded of the need for the study team to update all patient screening and recruitment data on EDGE (weekly as a minimum please).

Kind regards

Lou

Louise Hunn
Research Facilitator & RDU 1 Delivery Lead

NHS
Hull University Teaching Hospitals
NHS Trust

1

Appendix 24: Survival data

	Participant no'	Survival at 90 days	Survival at 180 days	Survival at 365 days	Days survival post screening
Group 1	1	N	N	N	34
	2	Y	Y	Y	>365
	3	Y	Y	Y	>365
	4	N	N	N	37
	5	Y	Y	Y	>365
	6	Y	Y	Y	>365
	7	N	N	N	29
	8	Y	Y	N	189
	9	Y	Y	Y	>365
	10	Y	Y	N	242
	11	Y	N	N	151
	12	Y	Y	Y	>365
	13	Y	N	N	87
	14	Y	Y	N	287
	15	Y	Y	Y	>365
	16	Y	Y	Y	>365
	17	Y	Y	Y	>365
	18	Y	Y	Y	>365
	19	Y	N	N	73
	20	Y	N	N	66
	21	Y	Y	Y	>365
	22	Y	N	N	68
	23	N	N	N	25
	24	N	N	N	38
	25	Y	Y	Y	>365
	26	Y	Y	Y	>365
	27	Y	Y	N	327
	28	Y	Y	N	216
	29	Y	Y	Y	>365
	30	Y	Y	Y	>365
Group 2	31	Y	N	N	165
	32	N	N	N	71
	33	Y	Y	Y	>365
	34	N	N	N	21
	35	N	N	N	40
	36	Y	Y	N	235
Group 3	37	N	N	N	48
	38	Y	Y	*	*
	39	Y	N	N	131

Key: Y – Yes, survival at set time point, N – No, deceased at set time point
*only 6-month follow up data available

By Alex Bullock, age 30