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Assessing the feasibility of dietary restriction, including short-term fasting, at the time of chemotherapy

Assessing the feasibility of dietary restriction, including short-term fasting, at the time of chemotherapy

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A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Health Sciences.

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Abstract

Background

Dietary restriction may help protect non-tumour cells from chemotherapy toxicity by allowing them to conserve energy for maintenance/repair. Most of the research to date has been conducted in cell line/animal models and efficacy of interventions in humans is not clear. It has not yet been determined whether people due to undergo treatment for cancer are able to adhere to dietary restriction interventions. The aim of this thesis was to assess the feasibility of dietary restriction interventions at the time of cancer treatment.

Methods

Three studies were conducted. A systematic scoping review of the literature was performed on dietary restriction at the time of cancer treatment. A Randomised Controlled Trial (RCT), with an embedded qualitative study, was designed to test the feasibility of a 36-hour short-term fast prior to chemotherapy for colorectal cancer. Behavioural change and interview data from a previous RCT of intermittent compared to continuous energy restriction in women receiving chemotherapy for breast cancer was synthesised in a mixed method study.

Results

The systematic review identified that energy restricted diets were tolerated well, however adherence was variable and there was a paucity of qualitative data on patient experiences. Recruitment to the feasibility RCT was delayed due to the COVID-19 pandemic and recruitment is ongoing. Analysis of behavioural change and interview data identified that social influences, dietary preferences, emotional eating, and low self-efficacy act as barriers to adherence.

Conclusion

The findings show limited research on dietary restriction interventions in humans to date. Issues surrounding recruitment and adherence to interventions may affect the feasibility of testing their efficacy. Potential barriers and facilitators of adherence have been identified. Future research should focus on addressing these barriers to improve adherence. Addressing issues with feasibility is required to ensure that the efficacy of dietary restriction can be fully assessed in future studies.

Covid-19 Statement

The Covid-19 pandemic led to the halt of all non-covid related research activity across the NHS. The SWiFT feasibility trial of short-term fasting, described in Chapter 3 of this thesis, was therefore suspended in March 2020. It reopened to recruitment in September 2020 at one site and will reopen at a second site in June 2021. As such, the trial remains ongoing at the time of writing this thesis, and the results are not available for inclusion. When the trial is completed, it will provide high quality data on the feasibility of the intervention, which will add to the findings of this thesis.

In lieu of this feasibility data, an existing, previously unanalysed, dataset from a trial of intermittent energy restriction compared to continuous energy restriction in women being treated for early breast cancer was used (Chapter 6). This provided an alternative data set to further study the feasibility of dietary restriction during cancer treatment.

Author's declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED:

DATE:

Integration of Publications Statement

Two chapters in this thesis include previously published work.

The systematic scoping review (chapter 3) has been published as a research article in the journal BMC Cancer[1]. This chapter includes the background (section 3.1), methods (section 3.2) and results (section 3.3) of the review, as published. The contributions of the authors were as follows: ES led the review and wrote the first draft of the manuscript. RP, CA, CP, GH and AN were involved in the design and concept of the review protocol. ES, RP, CA, AM and CE screened the data. ES, RP, and CA extracted the data. All authors reviewed and approved the final version of the manuscript.

The protocol for the randomised controlled trial described in chapter 4 has been published in Pilot and Feasibility Studies[2]. This chapter includes the methods (section 4.3) of the protocol, as published. The contributions of the authors were as follows: ES led the concept and design, development and set-up of the trial and wrote the first draft of the manuscript. All other authors were involved in the concept and design of the trial and reviewed the manuscript. All authors read and approved the final manuscript.

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Thank you also to my other colleagues at the BRC, especially Dr Clare England and Alex Mitchell for their input into SWiFT and the scoping review and to Stu Toms for CRF and database design and support.

I am also so grateful to the oncology research team at the University Hospitals Bristol and Weston NHS Foundation Trust whose input into the SWiFT trial was invaluable. Thank you also to the research team at The Christie NHS Foundation Trust for all their effort in setting-up, opening and running the SWiFT trial, in spite of all the additional pressures they have faced over the last year.

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Finally, I would also like to say a huge thank you to my family: my husband, Mum and sisters. Their encouragement, support and sense of humour have been a constant throughout.

This PhD is dedicated to the memory of my Dad, Patrick Hewitt. If I can continue into my post-PhD career with even a fraction of the compassion and confidence which he applied to his career and family life, I will be very happy indeed.

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Abbreviations

AC-T – Doxorubicin, cyclophosphamide, paclitaxel chemotherapy

AEs – Adverse Events

AM – Alex Mitchell, Transition Fellow in Nutrition

AN – Andy Ness, Emeritus Professor of Epidemiology, University of Bristol

ATP – Adenosine 5'-triphosphate

B-AHEAD 2 – The "Breast activity and healthy eating after diagnosis – 2, During chemotherapy for early breast cancer" trial

BHB – Beta-hydroxybutyrate

BMI – Body mass index

BRC – Biomedical Research Centre

CA – Charlotte Atkinson, Senior Research Fellow, University of Bristol

CAPOX – Capecitabine and Oxaliplatin chemotherapy

CE – Clare England, Senior Research Associate, University of Bristol

CER – Continuous energy restriction

CG – Control Group

CHO – Carbohydrate

CI – Confidence Interval

CP – Claire Perks, Associate Professor in Tumour Cell Biology and leads the IGF & Metabolic Endocrinology group in the Bristol Medical School

CRF – Case Report Form

CRP – C-reactive protein

CTCAE – Common Terminology Criteria for Adverse Events

DR – Dietary Restriction

DLTs – Dose-Limiting Toxicities

DNA – Deoxyribonucleic Acid

DSR – Differential Stress Resistance

DSS – Differential Stress Sensitisation

ES – Ellie Shingler

EQ-5d-5L – EuroQol Group 5-dimension health related quality of life instrument with 5 levels of response

FBC – Full Blood Count

FEC – Fluorouracil, Epirubicin, cyclophosphamide chemotherapy

FEC-T – 5 fluorouracil, epirubicin, cyclophosphamide, docetaxel chemotherapy

FFM – Fat Free Mass

FM – Fat Mass

FMD – Fasting Mimicking Diet

FT4 – thyroxine

GH – Georgia Herbert, Senior Research Associate, University of Bristol

GI – gastrointestinal

HbA1c – Glycated Haemoglobin

HPD – Highest posterior density interval

HR – Hazard Ratio

ICD – Immunogenic cell death

IER – intermittent energy restriction

IF – Intermittent Fast

IG – Intervention Group

IGFBP – Insulin-like Growth Factor Binding Protein

IGFs – Insulin-like Growth Factors

IMD – Index of multiple deprivation

IPAQ – International Physical Activity Questionnaire

IQR – Interquartile range

ISF – Investigator Site File

ISRCTN – International Standard Randomised Controlled Trial Number registry

KD – Ketogenic Diet

MDT – Multidisciplinary Team

MET – Methionine

MH – Michelle Harvie, Research Dietitian, University of Manchester

MRC – Medical Research Council

MRI – Magnetic Resonance Imaging

NHS – National Health Service

NIHR – National Institute for Health Research

NR – Not reported

OR – Odds ratio

pCR – Pathologic complete response

PEG – Percutaneous Endoscopic Gastrostomy

PRO-CTCAE – Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

PPI – Patient and Public Involvement

Ppts – Participants

PROM – Patient Reported Outcome Measures

QoL – Quality of Life

Quant – Quantitative Method

Qual – Qualitative Method

RCT – Randomised Controlled Trial

RECIST – Response evaluation criteria in solid tumours

RP – Rachel Perry, Senior Research Associate in Systematic Reviews

SAEs – Serious Adverse Events

SD – Standard deviation

SOP – Standard Operating Procedure

TMF – Trial Master File

TSH – Thyroid stimulating hormone

UHBW – University Hospitals Bristol and Weston NHS Foundation Trust

UK – United Kingdom of Great Britain and Northern Ireland

Y/S insulin receptor signal ratio – The ratio of pan-tyrosine (pY) to serine 312 phosphorylated (pSer312) insulin receptor signals

Chapter 1 BACKGROUND

1.1 INTRODUCTION

Fasting during the treatment for cancer is an area of growing research interest, due to the findings of pre-clinical research in animal, cell line and yeast models. This research has identified fasting as a potential tool for reducing the toxicities associated with cancer treatments such as chemotherapy and radiotherapy, as well as potentially improving tumour response and survival rates. However, although some studies of fasting during chemotherapy in pre-clinical models have shown promising results, it is unclear how well these findings translate to humans.

The aims of this thesis were to systematically review the literature on dietary restriction at the time of chemotherapy, to develop and test the feasibility of a short-term fasting intervention in people undergoing chemotherapy and to explore the feasibility of introducing energy restriction diets at the time of chemotherapy, using an existing dataset from a trial of dietary restriction in women being treated for breast cancer.

The thesis consists of three studies:

1. A scoping review of the literature on dietary restriction at the time of cancer treatment.
2. A feasibility randomised controlled trial (RCT) of short-term fasting prior to chemotherapy in people with colorectal cancer, including an embedded qualitative interview study to explore participant experiences of taking part in the trial.
3. A mixed methods analysis of behavioural change and participant interview data, collected during a previous RCT of intermittent energy restriction compared to continuous energy restriction in women receiving chemotherapy for breast cancer.

This chapter will outline the background and rationale behind the concept of dietary restriction at the time of cancer treatment. It will outline the biological mechanisms behind dietary restriction, focusing primarily on the findings from pre-clinical research, due to the paucity of studies in clinical populations. It will detail how cellular metabolism is affected in cancer and how this altered metabolism might be exploited, through dietary restriction, to help protect non-tumour cells against side effects of chemotherapy, while cancer cells remain susceptible to treatment. It will describe the, sometimes complex, relationship between weight change and chemotherapy, highlighting how dietary restriction

may need to be used with caution in some cancer populations, where weight loss could be detrimental to treatment outcomes. It will also describe the types of dietary restriction, in addition to fasting, that have been suggested as possible therapeutic strategies for reducing treatment toxicities.

1.2 CANCER

Cancer is one of the leading causes of death, globally, with the burden of disease expected to increase along with population growth[3]. In many high-income countries, it has now overtaken cardiovascular disease as the leading cause of death[4].

The development of cancer is a result of accumulated damage to cellular DNA, more specifically, to the genes which control cellular growth and programmed cell death, or apoptosis[5, 6]. Deregulation of these cellular systems which control cell growth and death, leads to uncontrolled cell growth and tumorigenesis[7].

Improved screening and detection techniques mean an increasing number of people are being treated for cancer[4]. Treatment for cancer depends on the site and stage of the disease, however surgery, chemotherapy and radiotherapy are the most common forms of treatment and each is associated with its own side effects[8]. Surgery is the surgical removal of tumorous tissue from the body. Side effects associated with this form of treatment can include wound infection, chest infection and blood clots[9]. Radiotherapy uses radiation to destroy cancer cell DNA. This can be external beam or internal radiotherapy. Depending on the site of the cancer, side effects can include weakness, sore skin and incontinence[10]. This thesis primarily focuses on the study of implementing dietary restriction interventions during chemotherapy treatment. Chemotherapy is a systemic form of treatment where cytotoxic drugs are administered that target cells during the process of cell division by damaging DNA and causing cell death[11]. Side effects vary depending on drug type and combination but common side effects include increased risk of infection due to reduced white blood cell production, nerve damage and gastrointestinal issues such as vomiting and diarrhoea[12].

As well as affecting patient experience and quality of life, treatment side effects from chemotherapy are of importance due to the potential for dose limiting toxicities (DLTs). The systemic nature of chemotherapy means that non-tumour cells within the body are also susceptible to damage from treatment. The mechanism of action of chemotherapy drugs is to target dividing cells. As cancer cells divide at a faster rate than normal cells, they are more susceptible to treatment[13]. However, so too

are non-tumour cells that are in the process of division. As chemotherapy is usually given as a course of treatment over a period of several months, damage to cellular DNA can accumulate in non-tumour cells, leading to symptoms which stop patients being able to continue treatment at the recommended dose. These symptoms are referred to as dose limiting toxicities and are defined as severe or prolonged side effects which limit or delay subsequent doses of systemic therapies[14, 15]. DLTs are assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) classification, whereby toxicities are graded in severity from 1 to 5, with grade 5 resulting in death. Toxicities classified as grade 3, or higher, are considered DLTs[15]. Common toxicities that can result in DLTs are immunosuppression caused by neutropenia, anaemia, thrombocytopenia, vomiting, and renal dysfunction. DLTs are clinically important as grade 3 or 4 toxicities can lead to subsequent delays or reduction in treatment dose, or chemotherapy being stopped before the planned number of cycles is completed. This in turn has the potential to reduce treatment efficacy [16]. For example, *in vitro* studies have found that for many chemotherapy drugs, the drug concentration in culture directly correlates with tumour cell death rate[17]. Similarly, reductions in dose intensity have consistently been found to be associated with lower tumour response rates in animal models, in multiple tumour types, where a 20% dose reduction reduced cure rates by 50% [17]. Clinical research has also found a strong relationship between reductions in chemotherapy dose and lower disease free survival as well as overall survival[17]. For example, in one retrospective analysis of 293 breast cancer patients, receiving at least 80% of planned dose was associated with a significantly better overall survival (HR = 2.61; 95% CI 1.44–4.73; p = 0.002) and disease-free survival (HR = 1.97; 95% CI 1.14–3.42; p = 0.02) than receiving less than 80%[18]. This relationship can be seen in other cancer types and chemotherapy agents. One study of patients with aggressive non-Hodgkin's lymphoma who received cyclophosphamide, doxorubicin, vincristine, prednisone chemotherapy found that those who received over 70% of intended dose intensity experienced increased 5-year survival rates compared with those receiving 70% or less[17]. Although these studies are limited by their retrospective design, they continue to build on the pre-clinical research and suggest that if dose intensity is not within the optimal range, there is the potential for reduced treatment efficacy. Together, these findings from pre-clinical and clinical studies suggest a dose–response relationship exists, which highlights the need for interventions that limit treatment toxicities without reducing treatment efficacy, with the ultimate goal of increasing response rates and survival.

In this thesis, two of the projects include specific cancer populations; the feasibility RCT looks at short-term fasting in men and women with colorectal cancer and the mixed method analysis looks at intermittent energy restriction compared to continuous energy restriction in women with breast cancer. These cancer types, and their common treatment regimens and associated DLTs, are described in further detail below.

1.2.1 Colorectal Cancer

Colorectal cancer was identified as one type of cancer that could potentially benefit from the introduction of a dietary intervention, aimed at reducing treatment side effects, in this thesis. Colorectal cancer, also referred to as bowel cancer, is cancer affecting the colon or rectum. It is the fourth most common cancer in the UK, with 41,300 new cases diagnosed each year[19]. Survival rates from colorectal cancer have more than doubled in the last 40 years and almost one in six people diagnosed in England and Wales survive their disease for ten years or more[19]. One of the main risk factors for developing colorectal cancer is age. In the UK, almost 18 out of 20 cases are diagnosed in those aged 60 and above. Other risk factors include family history, other digestive diseases such as Crohn's and ulcerative colitis and lifestyle factors[20]. In relation to lifestyle factors, for example, the World Cancer Research Fund has identified that being physically active and consuming a diet adequate in wholegrains, dietary fibre and dairy decreases the risk of colorectal cancer, while obesity and consuming red and processed meat increases the risk[21].

A standard treatment in the UK for stage 3 colorectal cancer (or stage 2 colorectal cancer that is at high risk of local recurrence) is surgical resection, followed by Capecitabine and Oxaliplatin (CAPOX) chemotherapy[22]. Oxaliplatin is a platinum-based drug which inhibits the synthesis of DNA, RNA and proteins, by forming covalent bonds between the platinum base and the DNA[23, 24]. Capecitabine is an example of an antimetabolite drug. This class of drugs are analogues of the metabolites required for DNA synthesis (i.e., they have similar chemical structure), and therefore interfere with a cell's ability to synthesise DNA by substituting themselves in place of the required metabolites[13, 23, 24]. CAPOX treatment cycles last 21 days, with oxaliplatin given via infusion on day 1 and capecitabine tablets taken orally, twice daily, on days 1-14, for at least 4 cycles. Previous research has shown that 57% of people receiving CAPOX required dose modifications due to toxicity[25]. Dose limiting toxicities for this combination regime include vomiting, diarrhoea and stomatitis[26]. Therefore, interventions which aim to limit toxicities in this treatment group are of considerable interest.

Colorectal cancer has not been studied in previous trials of short-term fasting during cancer treatment, as shown in the literature review detailed in Chapter 3. The paucity of dietary restriction research within this population, combined with the level of DLTs caused by the standard treatment for stage 2/3 colorectal cancer, confirmed that this would be a suitable population for a feasibility trial of short-term fasting at the time of chemotherapy.

1.2.2 Breast Cancer

Breast cancer is cancer which forms in the tissue of the breasts, the most common type of which forms in the lining of the milk ducts, known as ductal carcinoma[27]. Breast cancer is the most commonly diagnosed cancer in women worldwide, which equated to more than two million cases in 2018[28]. In the UK, breast cancer survival rates are improving, having doubled in the last 40 years. It is now estimated that three in four women in England will survive their disease for ten years or more[29].

The risk factors for developing breast cancer are varied and include age, genetics and lifestyle factors[29]. Regarding lifestyle related factors, research from the World Cancer Research Fund suggests that, for premenopausal breast cancer, there is strong evidence that vigorous physical activity, breastfeeding and being overweight or obese in adulthood, decreases risk, while consuming alcohol increases risk. For postmenopausal breast cancer, there is strong evidence that being physically active and breastfeeding decreases risk, while being overweight or obese through adulthood and consuming alcohol increases risk[30]. While the increased risk associated with body fatness in postmenopausal women is considered to be due to increased production of oestrogen by adipose tissue, reasons for the inverse association of body fatness in adulthood and breast cancer risk in premenopausal women are complex and not fully understood[31]. Few studies have included sufficient numbers of premenopausal women to confirm whether risks differ by other explanatory variables, or cancer subtype[31]. However, it is possible that differences in adolescent growth, growth hormone and sex hormone activities in relation to being overweight compared to normal weight in early adulthood may play a part in explaining the differences in risk factors[30]. In premenopausal women, those who are overweight have been found to have lower oestradiol levels than those who are normal weight, in some studies. For example, in one cohort of 436 premenopausal women, lower oestradiol levels were found in obese/overweight women compared with normal weight [32.8 pg/mL (95% CI: 30.6-35.2) vs. 39.8 pg/mL (95% CI: 37.0-42.8); $p<0.001$)][32]. However, evidence for this has been inconsistent, potentially due to variations in sample timing in relation to menstrual cycle[33]. A longitudinal study of breast cancer in 113,130 premenopausal participants in the Nurses' Health Study II found that the inverse association

between BMI and premenopausal breast cancer incidence was stronger for women with oestrogen receptor(ER)-positive breast cancer, than for women with ER-negative breast cancer (P for heterogeneity = 0.19) and authors suggest decreased blood oestrogen levels in obese premenopausal women may explain, in part, the inverse association with breast cancer[33]. Subsequent pooled analysis of premenopausal cohorts also found an inverse association between BMI and ER-positive but not ER-negative breast cancer in pre-menopausal women and similarly suggest that BMI-related differences in sex-hormone profile may explain the inverse association of BMI and breast cancer risk[34].

Treatment for breast cancer varies, depending on the type and stage of the disease. Breast cancer is often classified by whether the breast cancer cells have hormone receptors for oestrogen or progesterone[30]. Surgery and radiotherapy can be used to remove tumour mass, and neoadjuvant drug treatment may be used prior to this to reduce the size of the tumour. Adjuvant drug therapy can be used following surgery, to reduce the risk of recurrence or development of invasive disease and can include anti-hormone biological therapy as well as chemotherapy for hormone receptor positive cancers [35].

Anthracycline–taxane combination chemotherapy is the recommended adjuvant treatment for invasive breast cancer[35]. Anthracyclines are antibiotics which inhibits DNA replication[24, 36]. Taxanes are semisynthetic drugs which block cell cycle mitosis and induce apoptosis[24]. A commonly used regimen in the UK is FEC-Docetaxel, where epirubicin in the FEC forms the anthracycline component and docetaxel the taxane component. For this regimen, fluorouracil 500 mg/m2, epirubicin 100 mg/m2, and cyclophosphamide 500 mg/m2 (FEC) are given intravenously on day 1 of each 21-day cycle, for a duration of 3-4 cycles. This is followed by Docetaxel 100 mg/m2 which is given intravenously on day 1 of each 21-day cycle for a further 3-4 cycles. DLTs associated with this treatment include cardiotoxicity, nausea, vomiting, peripheral neuropathy and reduced immune function[24, 36, 37].

As will be discussed further in section 1.4.1, women being treated with chemotherapy for breast cancer were identified as a population that could benefit from energy restricted dietary interventions, due to the potential for this population to gain weight during treatment, and the associations between weight gain and poorer outcomes.

1.3 METABOLISM AND CANCER

1.3.1 Differences between tumour and non-tumour cells in their reaction to nutrient availability

When food is ingested, the hormone insulin is secreted by the islets of Langerhans cells within the pancreas. Insulin increases the uptake of glucose and fatty acids by body tissues, predominantly skeletal muscle and fat tissue, removing them from the blood stream[38]. This maintains metabolic homeostasis in the blood stream following a meal and provides cells around the body with the fuel required for cellular division and growth[39]. Growth factors also play a role in this process. These are extracellular ligands which act to reprogramme the metabolic pathways within cells based on nutrient availability, increasing nutrient uptake as required for proliferation and growth[40]. However, cancer is a disease associated with dysregulated metabolism and differences in metabolism exist between and tumour and non-tumour cells[41]. These include differences in relation to response to growth signals, energy sources and autophagic capacity, and are discussed in further detail below.

1.3.2 Response to growth signals

During times of nutrient scarcity, non-tumour cells have the ability, through evolutionarily conserved cell signalling processes, to switch from a state of proliferation to a state of maintenance and repair. This is a survival mechanism, which allows organisms to maximise their chance of survival by diverting energy for repair during periods of nutrient deprivation[42]. This is partially mediated by a reduction in glucose and insulin-like growth factors (IGFs)[6, 42]. IGF-1 is a growth factor which mediates the progression of cells from the G1 phase of cell division, which is a restricted growth phase, to S phase, where DNA replication occurs[43]. A reduction in IGF-1 reduces the activation of the downstream signalling pathways Ras/MAPK, and P13K/Akt that promote expression of genes involved in proliferation, growth, survival, and increased protein synthesis via the mTOR pathway (Figure 1-1). These altered pathways lead to a withdrawal of energy from growth/reproduction to maintenance/repair which in turn offers increased cellular protection[44, 45].

Two of the recognised hallmarks of cancer are the ability of tumour cells to continue to grow in the absence of growth factors and in the presence of growth inhibitory signals[7]. Mutated tumour cells evade these signals due to i) loss of function mutations in tumour-suppressor genes (Retinoblastoma (Rb), p53 and Phosphatase and Tensin Homolog (PTEN)) that leads to insensitivity to growth inhibitory signals and ii) gain of function mutations in oncogenes (Ras, Akt and Mechanistic Target Of Rapamycin Kinase (mTOR)) that culminates in proliferation pathways continually being active, even in the absence

of growth signals[44]. Therefore, tumour cells do not respond to nutrient deprivation in the same way as non-tumour cells and continue to proliferate, even when nutrients are scarce. This could potentially reduce their ability to protect and repair themselves in the absence of nutrient supply.

1.3.3 Energy source and metabolic adaptability

Most non-tumour cells favour the use of oxidative phosphorylation to produce adenosine 5'-triphosphate (ATP), the principle cellular energy molecule that is required to power cellular activities[46]. Glucose is used as the initial source of energy in the production of ATP by mitochondria. However ketone bodies and fatty acids can be utilised, when glucose is scarce[47].

Tumour cells are associated with increased glucose uptake and a reduced ability to adapt to reduced glucose availability, when compared to non-tumour cells[41]. Tumour cells are known to rely on glycolysis, rather than mitochondrial oxidative phosphorylation, for energy production. Glycolysis is the process used to create energy in the absence of oxygen and is a precursor to oxidative phosphorylation in most healthy cells. However, tumour cells use this form of energy production, even in the presence of oxygen[48, 49]. This phenomenon of fermenting glucose to form lactic acid in a process of aerobic glycolysis is coined the Warburg effect[50] (Figure1-1). The Warburg effect can be described as a trade-off of “catabolic efficiency for anabolic utility” as the products of glucose metabolism can be used for biosynthesis required for daughter cells during proliferation[51]. So, although glycolysis is more rapid at creating ATP, than oxidative phosphorylation, it is less efficient in terms of the amount of ATP created. Therefore tumour cells require large amounts of glucose to create the levels of ATP required for cell function[52]. This metabolic dysregulation is seen in nearly all tumour cells and means they are highly dependent on glucose availability. This may put tumour cells under increased pressure when nutrient availability is scarce and requires the cell to switch from glucose metabolism to ketone metabolism and fatty acid oxidation [53]. The metabolic adaptability of non-tumour cells which are able to utilise more substrates for energy than tumour cells, means they may have an increased likelihood of survival when nutrient availability is low, when compared to tumour cells[41].

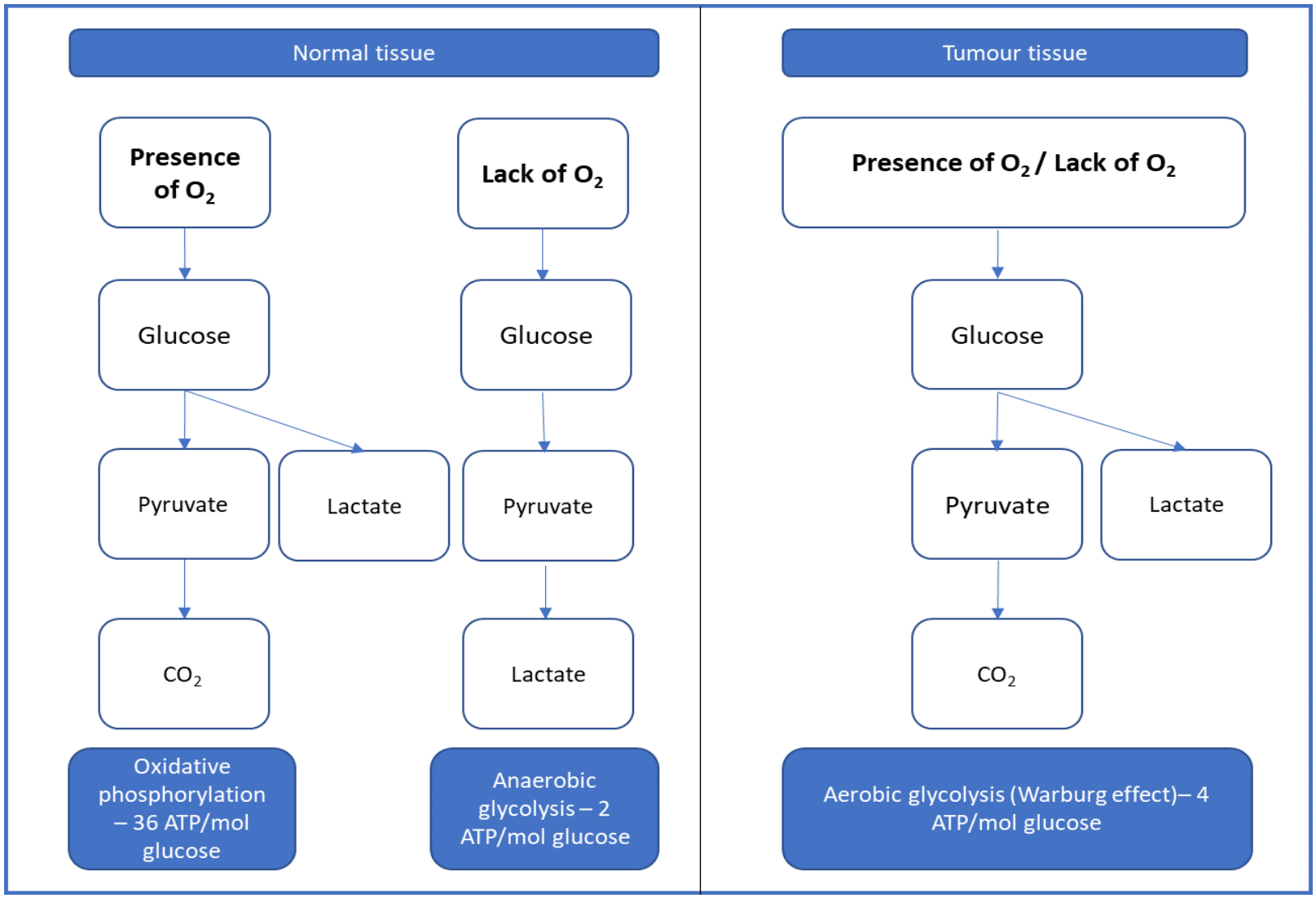

Figure 1-1 Difference in energy production between normal tissue and tumour tissue, adapted from Vander Heiden et al, 2009[48].
Abbreviations: ATP – Adenosine triphosphate; O_2 – Oxygen; CO_2 – Carbon dioxide

1.3.4 Autophagic capacity

A further disparity between the metabolism of non-tumour and tumour cells is their capacity to increase autophagy. Autophagy is the cellular process by which cells are able to degrade and recycle cellular components in order to maintain homeostasis[54]. The term autophagy translates to "eating of self" which describes the self-degradative activity that occurs [55]. Because a restriction in energy supply leads to a reduction in macronutrient supply, cells are required to maintain growth and repair without this supply of new macronutrients. Therefore, increasing autophagy allows protein aggregates and defective organelles to be degraded into constituent parts and recycled for energy production and repair. Energy restriction initiates this process by activating the enzyme AMP activated protein kinase (AMPK), which in-turn increases autophagy[51, 56](Figure1-2). Some biological therapies for cancer target autophagy, aiming to reduce autophagy to limit the ability of tumour cells to adapt and survive during treatment. There are therefore concerns about whether upregulation of autophagy, e.g., via dietary restriction, is similarly protective to cancer cells[53, 54]. However, cancer is often associated with a defect in autophagic capacity. Activation of the Akt and P13k pathways inhibits autophagy and while the PTEN gene would usually upregulate autophagy, mutations resulting in the loss of function of this tumour suppressor gene inhibit this corrective action[57]. Therefore, although autophagy occurs in tumour cells, the mutations present in the oncogenes and tumour suppressor genes that are seen in many cancer cells means that their autophagic capacity is limited compared to non-tumour cells[56]. A reduction in growth factors through nutrient deprivation may therefore lead to upregulation of autophagy in healthy cells but not in tumour cells, producing an increased protective effect in non-cancer cells.

1.3.5 Differential stress resistance

These differences in reaction to nutrient scarcity between healthy and tumour cells collectively lead to a concept which has been referred to as differential stress resistance (DSR). Figure 1-2 outlines how the altered cellular pathways induced by nutrient restriction, lead to reduced proliferation and "recycling" of cellular constituents in healthy cells, but not tumour cells. Within normal cells, the downregulation of the Ras/MAPK and P13k/Akt pathways leads to both a reduction in cell proliferation and an increase in apoptosis, while upregulation of the AMPK pathway increases autophagy. Together, these mechanisms lead to increased cellular protection because energy can be reserved for cellular maintenance and repair, using recycled materials made available due to increased autophagy. Within tumour cells, Ras/MAPK and P13k/Akt pathways avoid down regulation signals due to oncogenic mutations, allowing

cells to continue to proliferate. The alteration of the P13k/Akt pathway is one of the most frequently mutated pathways in cancer and is seen in a wide range of cancer types[58]. As chemotherapy targets dividing cells, DSR may allow tumour cells to remain susceptible to the effects of chemotherapy while at the same time helping to protect healthy cells against the toxic effect of chemotherapy[59]. Therapeutic regimes that take advantage of this concept of DSR are therefore of interest as a potential tool in the treatment of cancer.

Due to the potential effects of energy restriction on non-tumour cells, and the unique metabolic changes that cancer cells undergo, dietary restriction is one form of intervention which has potential to be utilised during cancer treatment, to limit treatment side effects. As previously discussed, chemotherapy is a systemic form of treatment, which targets proliferating cells. This means that non-tumour cells that are in the process of division, are also affected by treatment and it is the damage to healthy cells which causes side effects associated with chemotherapy. Therefore, offering increased protection through DSR, could reduce proliferation in these cells and ultimately offer increased protection from chemotherapy side effects. For example, fasting has been found to reduce chemotherapy-induced vomiting in cancer-bearing dogs receiving doxorubicin chemotherapy and to protect against weight loss, diarrhoea and leukopenia in mice receiving irinotecan chemotherapy[60, 61]. The authors hypothesise that the increased protection in fasted animals was due to DSR, induced by fasting. These findings are consistent with other studies in mice, which identified more significant chemotherapy related adverse events and leukopenia in mice fed *ad libitum* diets, compared to mice that were fasted for 48-72 hours[62].

Furthermore, pre-clinical research has found that when used in combination, nutrient starvation alongside addition of chemotherapy drugs has promoted DNA breaks in cancer cells[11]. This has been shown across multiple cell line models using multiple chemotherapeutic agents[11]. The Authors of that study were also able to offer a potential mechanism behind the DNA damage by measuring levels of oxidation in breast cancer cells treated with chemotherapy under starved and fed conditions. Their findings showed that levels of oxidative stress, which leads to DNA damage, were higher in breast cancer cells being treated under starved conditions than in cells under normal conditions. These findings suggest that cells treated under fasted conditions promote oxidative stress in tumour cells. Further studies in animal models also found evidence of increased sensitisation to chemotherapy under fasting conditions. When mice bearing melanoma tumours were treated with doxorubicin and cyclophosphamide chemotherapy, greater therapeutic effects were found in fasted mice, compared to

control[63]. Similarly, studies of murine models of human lung cancer found no effect of tumour growth when treated with cisplatin chemotherapy alone but found a 65% reduction in tumour volume three weeks after treatment with both short-term fasting in combination with cisplatin[64]. In this way, preclinical studies suggest that energy restriction has the potential to sensitise tumour cells to cytotoxic treatment, as well as offering increased protection of non-tumour cells. This phenomenon means that reduced glucose availability puts tumour cells which rely on glycolysis to meet their energy requirements, under increased stress, allowing chemotherapy to cause more DNA damage and apoptosis in tumour cells, has been referred to as differential stress sensitisation (DSS)[65]. Although, as discussed previously, these results cannot be directly extrapolated to humans, they provide a plausible biological mechanism behind the potential benefits of implementing dietary restriction during cancer treatment, and a rationale for further study of these interventions in human populations. The studies to date also do not provide evidence for the optimal timing or duration of fasting interventions in humans.

Diets such as short-term fasting and ketogenic diets are methods of dietary restriction which aim to exploit this difference in energy metabolism[66]. These diets, and their effects on DSR, are detailed in section 1.4, below.

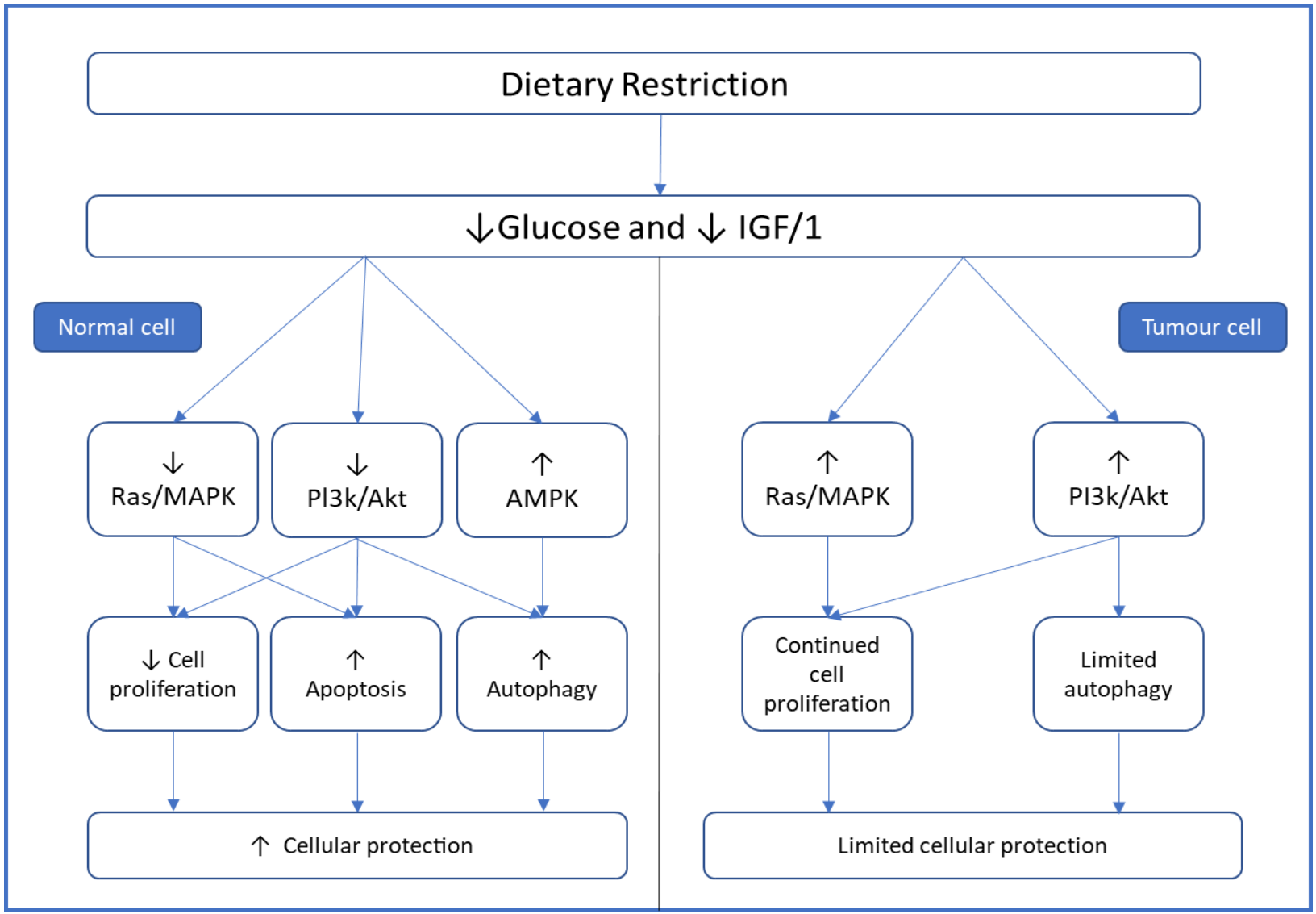

Figure 1-2 A model for the mechanisms of Differential Stress Resistance, adapted from Lee & Longo, 2011 [44]

1.4 Dietary Restriction

Although, as discussed previously, diet may influence treatment toxicities, as well as treatment efficacy in patients undergoing chemotherapy, dietary recommendations from healthcare professionals and cancer support institutions are often inconsistent and vague and previous research has identified a need for evidence-based nutritional guidelines[60, 67, 68]. For example, one study of online recommendations from websites associated with a large cancer network, found that half of the websites included in the review recommend a low-fat diet for weight maintenance, while the other half recommend an energy-dense diet, often advocating the consumption of high-fat foods, for weight maintenance[67]. Although this study was published in 2013, and dietary information provision may have improved since the study was conducted, more recent research suggests it is still an ongoing issue. One prospective longitudinal cohort study of 872 adults with non-metastatic colorectal cancer, published in 2021, found that approximately a third of participants wanted more dietary advice, while only a quarter of participants reported having received dietary advice[69]. This may be due, in part, to a lack of evidence and training provided to healthcare professionals on nutritional requirements during treatment. An online survey of 584 health care professionals working in oncology in the UK between June 2016 and May 2017, found that 77% of respondents provided cancer patients with information on nutrition. However, only 20% were completely confident in providing dietary advice. In addition to this, 65% of respondents reported they had a need for training on nutritional care for cancer patients, including evidence for alternative dietary approaches (57% of respondents)[70]. Taken together, these studies suggest that while some dietary advice is available to patients, there is the potential to improve provision of advice to oncology patients, while healthcare professionals are also interested in receiving further information and training on alternative dietary approaches for their patients.

As discussed in section 1.3.5, some evidence, primarily from lab-based studies, suggests that dietary restriction may lead to the increased vulnerability of tumour cells to treatment through mechanisms such as decreased growth signalling for healthy cells and the lack of metabolic adaptability found in tumour cells.

A growing body of evidence highlights how diet and nutrition can affect the biological processes in both the development and progression of cancer cells[71]. Findings from the field of ageing research have implicated energy intake in the biology of ageing[72]. Excessive energy consumption leads to an increase in the amount of reactive oxygen metabolites generated in cells. This leads to the cellular damage that is responsible for ageing and ageing related illness[73]. Since the 1990s, energy restriction without malnutrition has been widely researched as a form of intervention to delay the aging process in model organisms, with the aim of increasing lifespan[57]. For example, one study found a 50% reduction in cancer and cardiovascular disease in primates following a chronic 30% energy restricted diet for their adult lifespan[72]. The potential protective effect of energy restriction on age-related chronic diseases such as cancer found in these pre-clinical studies has led to a growing interest in the use of energy restricted diets as an adjuvant treatment for cancer. The increased lifespan and resistance to stress seen during these pre-clinical studies, means there is also an interest in the use of energy restriction to protect the body against toxic effects of cancer treatments such as chemotherapy and radiotherapy[59]. However, when used for people undergoing treatment for cancer, the impact of energy restriction on weight change must be considered.

1.4.1 Weight change during chemotherapy

The relationship between weight change and cancer treatment varies between cancer types.

For example, in colorectal cancer, body weight has been found to decrease following surgery, then increase during and following chemotherapy[74]. Although weight gain is more common than weight loss in people receiving adjuvant chemotherapy for colorectal cancer, weight loss in this group has also been associated with increased mortality in some[75, 76], although not all studies[77]. One retrospective study found that for every 5% loss of baseline weight, there was a 41% increased risk of colorectal cancer–specific mortality (95% CI:29%–56%), while weight gain was not associated with colorectal cancer–specific mortality (HR: 0.93, CI:0.63-1.37, p-value: 0.54).

Weight gain is also common in women receiving adjuvant chemotherapy for breast cancer[78] and has been found to be greater in premenopausal women and those with more advanced disease stage[79-81]. Reasons for weight gain may be due to reduced energy expenditure at this time, along with the failure of women to reduce energy intake to compensate for this decreased requirement[82]. However, unlike the findings in colorectal cancer which highlight weight loss, but not weight gain, as a risk factor for increased mortality, weight gain in

breast cancer treatment is associated with greater mortality[83, 84]. One cohort study of 3,993 women aged 20 to 79, with invasive breast cancer, found that each 5-kg of weight gain was associated with a 12% increase in all-cause mortality (P = 0.004) and a 13% increase in breast cancer-specific mortality (P = 0.01)(results were adjusted for weight, age, stage and menopausal status)[84]. Dietary restriction in this population could therefore aim not just to reduce treatment toxicities, but also to aid weight loss to improve outcomes.

These differences between cancer populations highlight that, while dietary restriction that leads to weight loss may be beneficial in some groups (e.g., breast cancer), chronic energy restriction may not be suitable for all people undergoing treatment with chemotherapy (e.g., colorectal cancer). Diets which restrict energy intake during cancer treatment must therefore be carefully designed to suit the population of interest, ensuring that weight is maintained, where required, and only lost where it is appropriate to do so.

This is in part due to concerns about inducing or worsening conditions such as cachexia and sarcopenia, which people with cancer are at an increased risk of developing [44, 53]. Cachexia is a syndrome associated with involuntary and progressive weight loss caused by the metabolic changes and systemic inflammation that are associated with cancer aetiology[87]. Metabolic changes, including increased energy expenditure, result in the body utilising skeletal muscle and adipose tissue for energy, leading to loss of body weight. This weight loss has found to be associated with shorter survival rates in cancer patients, and is considered an important prognostic factor[85]. While cachexia is defined as ongoing loss of skeletal mass, either with or without loss of fat mass[86], sarcopenia is defined as low skeletal muscle mass, in particular, alongside reduced grip strength and gait speed. It is associated with reduced overall survival and higher-grade treatment toxicity in people receiving treatment for cancer[87]. For example, one study of people receiving anthracycline-taxane chemotherapy for stage 1-3 breast cancer, found that with every five-unit decrease in skeletal muscle index (a measure of total skeletal muscle area divided by height), the risk of high grade (grade 3 to 5) toxicity increased by 27 % (RR: 1·27 (95 % CI: 1·09, 1·49), P = 0·002)[88]. Increased chemotherapy toxicity has also been seen in a range of advanced cancers including breast, liver, lung, colorectal and thyroid[89]. This increase in toxicities due to sarcopenia may be caused by changes to the metabolism and clearance of chemotherapeutic drugs in the body[89]. Sarcopenia may be caused by higher energy expenditure, inflammation and altered metabolism (i.e., increased energy expenditure and catabolism of skeletal muscle mass) that is associated with disease progression. Side effects of cancer therapy such as nausea and vomiting can exacerbate this issue due to reduced calorie

intakes[87]. There is some evidence in non-human primates that severe energy restriction may actually have beneficial effects on sarcopenia by reducing mitochondrial and oxidative stress[90]. However, data on the impact of short-term energy restriction on sarcopenia in people with cancer are lacking. Sarcopenia may be a risk associated with energy restriction in people with cancer if energy restriction is found to negatively affect skeletal muscle mass. One approach to minimise this risk would be to exclude people being treated for cancer with a low body mass index (BMI) from dietary restriction interventions. However, this may mean that those with sarcopenic obesity are still included (i.e., high BMI but low skeletal muscle mass) [91].

Prolonged periods of energy restriction have the potential to exacerbate weight loss associated with cachexia and sarcopenia. For example, there are concerns that dietary restriction could lead to reduced skeletal muscle mass, alongside sarcopenia, or compound the negative protein and energy balance associated with cachexia[86]. Therefore, alternative dietary approaches to chronic energy restriction have been suggested which aim to ameliorate the potential issues of weight loss and sarcopenia resulting from energy restriction. These approaches can be collectively defined as forms of dietary restriction (DR)[57] and are described in sections 1.4.2 to 1.4.5, below. Full details of the research conducted in humans, to date, on each of these forms of DR are presented in Chapter 3.

1.4.2 Short-term fasting

Short-term fasting at the time of chemotherapy has been suggested as one form of DR with the potential to induce DSR without the limitations of potential weight loss associated with chronic energy restriction[57]. Fasting cycles usually last over 24hrs and are separated by periods of normal eating, and they can be described as intermittent or periodic fasts[57]. A single 12 hour fasting interval can lead to a transient reduction in blood glucose and insulin levels[93] and IGF-1[94]. However, the optimal level and duration of fasting required to induce DSR has not been established. Varying degrees of fasting can be implemented, ranging from fasts based on reduced calories, such as in the 5:2 diet which restricts energy consumption to 20-25% of energy needs for two days per week and *ad libitum* consumption for the remaining five days, or complete abstinence of food, such as in water only short-term fasts[60, 93].

A systematic review published in 2017 on the effects of fasting on chemotherapy side effects and tumour progression identified 22 studies of short-term fasting which included 18 animal studies (mice and dogs), three human studies and one study which included both animal model and

human cell research, published between 2002 to 2016. The 19 animal studies were all RCTs and included a broad range of cancer types and tested fasts ranging from 24-72 hours in the majority of trials. The three human studies identified included one RCT, one dose-escalation study and one case series report. All of these included small sample sizes (n= 10-20). None of the human trials included qualitative research to conduct, for example, an in-depth review of aspects such as acceptability and tolerability of the interventions. Fasting lengths were varied, ranging from 24-180 hours and were followed for variable numbers of chemotherapy cycles (n = 1- 8). The review authors concluded that fasting reduced chemotherapy side effects such as vomiting and diarrhoea and reduced bone marrow suppression in a broad range of tumour types and chemotherapy regimens[61]. However, these results must be interpreted with caution, as most of the data reviewed was from animal research and differences exist between animal models and humans in relation to glucose control, tumour mass and relative bodyweight loss in response to dietary restriction[95]. It is therefore not clear how applicable these results are to humans, as responses in humans may differ to those seen in animal models. Two of the studies in humans reported less chemotherapy toxicities in 72hr fasts when compared to 24hr fasts[17, 18] which led the review authors to conclude that a 24hr fast may not be long enough for the protective effects of fasting to apply. In addition, although the authors acknowledged that the studies in humans were small, early scale studies, none of the studies directly assessed whether fasting would be feasible to implement in larger scale trials. For example, recruitment and adherence levels were not discussed in the review. Overall, their review provides some justification for the need for future research into short-term fasting, as it provides evidence from preclinical studies that suggests dietary restriction has the potential to protect against chemotherapy-induced toxicities. However, it also highlights the paucity of research in humans, and that further work is required to establish what level of restriction people receiving cancer treatment are willing and able to adhere to.

Due to this, questions still exist around how best to implement short-term fasting in cancer populations if the effects on outcomes of treatment are to be elucidated. For example, it is not yet clear what length of fast would be required to induce DSR in people receiving chemotherapy, and the dose-effect relationship remains unclear[95]. It is also not known for how long people receiving cancer treatment would be able to adhere to each fasting cycle, or for how many cycles they would be able to maintain adherence. Normal metabolic processes within the body may hinder adherence. The insulin secretion associated with food consumption begins prior to eating. This is called cephalic insulin as it is released in

response to food related stimuli such as sight and smell of food as well as time of day. As cephalic insulin secretion removes blood glucose from the blood stream, it may stimulate greater appetite if ingestion of food does not occur in the short-term, creating a potential challenge to adherence[39]. Poor adherence to short-term fasts could in turn limit the efficacy of an intervention and further feasibility research is warranted to address these questions.

1.4.3 Fasting mimicking diets

More recently, a fasting mimicking diet has been developed which mimics the physiological effect of fasting i.e. reduced blood glucose, IGF-1 and increased ketones[96], without having to reduce daily energy intake below 725kcal. This diet aims to overcome some of the difficulties of short-term, water only fasting, such as issues with adherence, adverse effects and malnourishment[96]. In humans, the most commonly studied fasting mimicking diet in healthy people spans five days each month and constitutes a strict, plant-based diet with one day consuming 1090 kcals (10% protein, 56% fat 34% carbohydrate) followed by four days consuming 725 kcals (9% protein, 44% fat and 47% carbohydrate). One crossover trial of 100 healthy adults comparing 3 cycles of FMD with usual diet, found a decrease in IGF-1 concentrations of 21.7 ± 46.2 ng/ml ($p = 0.0017$) between groups[97]. No grade 3 or higher toxicities were reported in either group. However, no differences were found between groups in terms of fasting glucose, triglyceride or cholesterol. To study this further, the authors conducted a post-hoc analysis, using baseline levels of risk factors to stratify participants into "normal" and "at-risk" subgroups for these measures. Their analysis found that FMD did not change fasting glucose levels for participants with baseline levels $\leqslant$99 mg/dl but was reduced by 11.8 $\pm$ 6.9 mg/dl in participants with baseline fasting glucose >99 mg/dl ($p < 0.01$). Similarly, triglyceride levels were reduced more in participants with baseline levels >100 mg/dl ($p = 0.0035$) and cholesterol was reduced more in participants with total cholesterol higher than 199 mg/dl at baseline ($p = 0.015$). These results suggest that FMD was more effective at inducing changes in these measures in at-risk populations. However, as these findings are based on a post hoc analysis in generally healthy participants, further research in participants with high glucose and cholesterol, using more robust research design such as RCTs is required. The study also reported a high rate of withdrawals/exclusions. 25% of participants in the FMD phase were excluded or withdrew from the trial. One quarter of these (n=6) were due to dislike of the diet and/or non-adherence to the dietary protocol. Other reasons for exclusion/withdrawal included "scheduling conflicts" (n = 11) and "personal issues" (n = 7).

In mice, a four day variation of the fasting mimicking diet was found to be as effective as two days of short-term starvation at retarding tumour growth and reducing IGF-1[98]. However, trials in humans, where the diet is being followed concurrently with chemotherapy, are currently ongoing and are summarised in Chapter 3 (section 3.3.2)[99]. Therefore, it is still unclear how well these findings in pre-clinical models translate to findings in human subjects. Results from the study in non-cancer human populations also suggests adherence may be an issue with the FMD[97]. Whether people undergoing treatment for cancer would struggle to adhere to the FMD due to the additional burden of their treatment, or, conversely, be more motivated to adhere due to the potential positive impact on their treatment, also remains to be seen.

1.4.4 Ketogenic diets

As well as energy restriction, the composition of restricted diets may also be of importance. Ketogenic diets (KDs) are diets high in fat with restricted carbohydrate intake and aim to switch the body's energy source from glucose metabolism to ketone metabolism. KDs can take several formats including a 4:1 or 3:1 ratio of fat to protein/carbohydrate, where the higher the ratio, the lower the amount of carbohydrate and protein. Higher ratios may therefore lead to higher levels of ketone metabolism (ketosis) [100].KDs are of interest because they simulate many of the physiological responses of energy restriction. These include a reduction in glucose and IGF-1 coupled with an increase in ketones that may impair the ability of tumour cells to repair DNA damage following treatment with radiotherapy or chemotherapy [53, 66]. KDs result in a shift from cells using glucose for ATP production, to using ketone bodies. As previously discussed (in section 1.3.3), metabolic changes in cancer cells mean they have adapted to favour the use of glycolysis rather than oxidative phosphorylation for energy production. These metabolic adaptations may limit their ability to use ketone bodies for energy in the same way as non-tumour cells, increasing stress on tumour cells when people follow a ketogenic diet. Preclinical studies in murine models support this as KDs have been found to reduce tumour growth in both breast and gastric cancer models[101, 102]. KDs may therefore potentially be used to exploit this inflexibility in substrate use for energy in tumour cells, to increase protection of non-tumour cells while increasing stress on tumour cells during treatment[103]. However, as previously discussed, it may not be appropriate to extrapolate these preclinical results directly to human populations. For example, as KDs are very different from a standard western diet, adherence to a KD may be challenging [100]. Issues with adherence may mean the same results are not observed in humans. Furthermore, KDs require a longer-term commitment from participants, compared to either the short-term fasts and FMD, to achieve

and maintain the metabolic changes required for DSR. This could in turn impact adherence to these diets, as participants would need to be able to maintain adherence over longer periods. The levels of adherence to these diets in cancer populations will explored further in Chapter 3.

Length of time on the diet needed to achieve metabolic effects may also impact adherence, and when used in combination with cancer treatment, the required length of ketogenic diets would be dependent on treatment type and length. This could make KD feasible in some cancer populations but more challenging in others. For example, one systematic review of the use of KDs as a complementary therapy to standard anticancer treatment found that the duration of interventions ranged from 0.5 to 31 months[104]. This review identified 11 studies, including a total of 102 participants. It also identified that changes in blood glucose when following the KD were inconsistent; of the ten studies that reported this measure, four reported a reduction in blood glucose, five reported no significant changes and one reported issues with maintaining low glucose levels. Poor adherence to diets could attribute to the variation in glucose reduction between studies. Also, the authors highlight that level of carbohydrate varied between interventions, with intake as high as 70g/day. So, although there is a plausible mechanism behind the use of KDs alongside cancer treatment, further research into adherence and the potential for diets to incite metabolic changes during treatment in humans is required.

1.4.5 Protein restriction

Protein restricted diets aim to reduce either overall protein intake or specific amino acids. For example, methionine is an essential amino acid that has been recognised to have an important role in cancer cell metabolism. As the only sulphur containing essential amino acid, it is required for synthesis of all other, non-essential sulphur containing amino acids and their derivative proteins[105, 106]. It is also required for DNA methylation, the process by which DNA gene modifications occur to alter gene expression[105, 107]. Other examples of amino acids that have been identified *in vitro* as important to metabolism in cancer cells are serine and glycine[108]. Placing cells under metabolic stress by reducing protein intake or removing specific amino acids from the diet could therefore be a potential therapeutic strategy for use alongside standard treatment.

Epidemiological research has found that people following energy unrestricted plant-only diets, with lower amounts of protein, have lower IGF-1 concentrations than those on long-term severe energy restricted diets with adequate nutrient intake[72]. This has led to an interest in protein

restriction as another diet with the potential to reduce IGF-1, with the aim of initiating DSR. One study comparing 21 people consuming a low protein, low energy diet to 21 people consuming a Western diet found that IGF-1 concentrations were lower in those eating the low protein/energy diet (139 +/- 37ng/ml) compared to those eating the Western diet (201 +/- 42ng/ml) ($P<0.005$) and that plasma IGF-I concentration correlated linearly with dietary total protein intake ($r = 0.498$, $P = 0.036$) in the Western diet group[109]. This reduction in IGF-1 on low protein diets may be due to decreased production of IGF-1 as well as increased clearance of IGF-1 from the blood stream into tissue, where it conserves tissue protein by inhibiting tissue protein degradation[109-111]. As well as a reduction in IGF-1, a further mechanism by which protein restriction may increase cellular protection is by the downregulation of the mTOR pathway caused by a reduction in amino acid availability[99]. As discussed in section 1.3.5, the mTOR pathway plays a role in protein synthesis and downregulation of this pathway will, in turn, lead to a decrease in cell proliferation and growth.

1.5 SUMMARY

Cancer is a disease of uncontrolled cell growth which is associated with altered metabolism in affected cells. It is a leading cause of death worldwide, with an increasing number of people being treated for the disease due to population ageing and growth as well as advancements in diagnosis and treatment options. Some of the mainstays of cancer treatments, such as chemotherapy and radiotherapy, can result in dose limiting toxicities, which in turn may reduce treatment efficacy. Interventions which aim to reduce treatment toxicities are therefore of interest for improving outcomes.

Pre-clinical research in cell line and animal models has shown that when nutrient availability is restricted, normal cells will alter their metabolic pathways through a complex cell signalling process to conserve energy for maintenance and repair. The genetic changes associated with tumour cell development allow cancer cells to continue to proliferate, even when energy is restricted. This limits their ability to conserve the energy required for maintenance and repair during times of stress. This creates a phenomenon known as DSR between tumour and non-tumour cells, whereby tumour cells may be more susceptible to stress induced by cytotoxic treatments, such as chemotherapy, than non-tumour cells.

Restricting energy and/or nutrient availability through dietary restriction is therefore a potential tool to use during treatment of cancer to help selectively protect non-tumour cells from cytotoxic treatment. In some population groups, such as those undergoing chemotherapy for breast cancer, it may also be a useful tool to aid weight loss and improve longer term survival. However, chronic energy restriction is limited in its use due to potential issues with weight loss and muscle loss in other cancer populations. Energy restriction through short-term fasting and diets which mimic the effects of fasting may induce metabolic changes that provide a protective effect over healthy cells, while limiting the negative effects of long-term energy restriction in populations for whom weight loss is detrimental. However, as much of the research to date has been conducted in pre-clinical settings, it is not yet clear how feasible these interventions are in human populations during cancer treatment.

The aim of this PhD is to explore the feasibility of energy restricted diets in people undergoing chemotherapy. It will summarise the current literature on dietary restriction and cancer treatment in humans through conducting a systematic scoping review. This will in turn inform the development of a feasibility RCT of short-term fasting prior to CAPOX chemotherapy in people with colorectal cancer, including an embedded qualitative study to further explore the experiences of trial participants. Finally, a mixed methods analysis will be conducted on data from a previous RCT of intermittent vs continuous energy restriction in women receiving chemotherapy for breast cancer.

The thesis will address gaps in knowledge around the feasibility of implementing dietary restriction interventions during chemotherapy, so that the findings can be used to inform further research of dietary restriction during cancer treatment.

Key Messages
1. Cancer is a disease associated with dysregulated metabolism. 2. Differential Stress Resistance (DSR) is the concept of increased protection of normal cells, while cancer cells remain susceptible to cancer treatment, through metabolic changes induced by a reduction in nutrient availability.

3. While some studies of dietary restriction during chemotherapy in pre-clinical models have shown promising results, with reductions in cellular toxicity and improvements in chemotherapy efficacy, it is unclear how well these findings translate to humans.
4. Although suitable for some populations, long term energy restriction may not be practical for people receiving treatment for some forms of cancer, due to their increased susceptibility to weight-loss, sarcopenia and cachexia.
5. Dietary restriction methods such as short-term fasting, fasting mimicking diets, ketogenic diets and protein restriction aim to induce DSR, without the potential negative impacts of chronic energy restriction.
6. The aim of this thesis is to explore the feasibility of conducting trials of dietary restriction, including short-term fasting and intermittent energy restriction, during chemotherapy.

Chapter 2 METHODOLOGY

As discussed in Chapter 1, the aims of this research thesis are to systematically review the literature on dietary restriction at the time of chemotherapy, to develop and test the feasibility of a short-term fasting intervention in people undergoing chemotherapy for colorectal cancer, to qualitatively assess patient experiences of that intervention, and to understand some of the behavioural aspects of, and potential barriers and facilitators to, following a restricted diet at the time of chemotherapy using data from a previous trial of intermittent fasting during chemotherapy for breast cancer.

This chapter will describe the philosophical approach to the research and the conceptual framework used to shape it. It will outline the three projects which comprise the thesis and the methodology used within each project. It will discuss why mixed method research was an appropriate design to address the questions raised in this thesis and outline how it ties in with the adopted philosophical approach. Finally, it will detail how the mixed methods designs were applied to the projects that comprise the thesis.

2.1 PHILOSOPHICAL ASSUMPTIONS

Research paradigms are a way of defining the social settings for research, in which research communities hold shared beliefs about which questions are meaningful and which methods are appropriate in trying to answer those questions. They outline the set of beliefs which guide a research community's actions[112].

All research paradigms reflect a set of philosophical assumptions held by the researcher(s) undertaking the studies[113]. These assumptions shape how the research question is framed, and the techniques chosen to answer those questions. They detail the researcher's ontological and epistemological perspectives, where ontology is concerned with what constitutes reality and epistemology is concerned with what constitutes knowledge or understanding[114].

This thesis draws on two complementary research paradigms: post-positivism and pragmatism. To understand these paradigms, it is useful to consider them within the context of preceding or alternative paradigms. The traditional paradigm of positivism laid the foundations for research into the natural and social sciences. It assumes that the scientific method is the sole way of learning the truth about the world, both physical and social[115]. Positivist inquiry assumes that an objective reality exists which can be verified through observation. Within this paradigm, the researcher is an objective observer of these external truths. It therefore assumes that the researcher has the ability to remain unbiased and neutral in their observations[116]. It also does not allow for the measurement of unobservable variables, that cannot be directly perceived. For this reason, the positivist perspective has been strongly critiqued[117].

In response to these issues, a refined version of this perspective emerged called the post-positivist paradigm. Post-positivism is an ontological and epistemological perspective that accepts, like the positivist view, that there is an objective reality that can be studied and reported. It advocates the use of scientific method to study that reality. However, unlike the positivist view, it recognises that there is no absolute truth, as knowledge about the world is subjective and open to multiple interpretations[118]. The analogy used by Cohen *et al,* 2018, is a useful tool for understanding the post-positivist perspective. They suggest that if two people are sitting in a classroom, one at the front and one at the back, both people are still viewing the same classroom (i.e. the objective reality) however what they see is not necessarily the same, they view things differently because they are seated in different positions in the classroom (i.e. multiple truths about that objective reality can exist)[118]. Post-positivism, when applied to the question of the feasibility of dietary restriction interventions, is therefore useful in representing and taking into account the "lived experience" of those taking part in the trial and intervention[119], while at the same time acknowledging that the effect of fasting can be measured and studied through a well-designed randomised controlled trial (RCT).

The second research paradigm underlying this research is that of pragmatism. The concept of pragmatism shifts the emphasis away from the more abstract issues of epistemology and ontology. Instead, it focuses on the more contextual human experience. It is our previous experiences, and the beliefs that we have garnered from those experiences, that are more likely to guide our line of inquiry within research[112]. Unlike other research paradigms which advocate the use of one research method as superior to other methods (e.g. positivist paradigm and quantitative methods), pragmatism does not focus on what research perspective or method is "correct," but puts the focus on workable approaches which

address that particular research question[118]. Because of this focus on the research question being asked, rather than on the method alone, it allows for multiple methods/forms of data collection to be employed to answer the research question[120]. Pragmatism also allows the researcher to move between inductive and deductive approaches, where inductive research uses participant views to build themes and generate theory, and deductive theory analyses data to test hypothesis drawn from established theory[120, 121]. Furthermore it allows the researcher to move between subjectivity and objectivity[120].

This flexibility is useful when trying to understand the feasibility of implementing dietary restriction interventions during cancer treatment, as it allows the topic to be studied from an holistic point of view, both from the perspective of objective RCT outcomes and also the more subjective participant experience of undertaking these diets during their treatment. As will be discussed in further detail in this chapter, this need to develop an holistic understanding of the feasibility of dietary restriction intervention means the topic lends itself to a pragmatic approach and can benefit from the use of mixed methods to give an holistic view of how feasible it would be to implement trials of dietary restriction during chemotherapy.

These two paradigms, post-positivism and pragmatism, complement each other. Post-positivism can be described as being anchored in pragmatism because it recognises that there may be numerous ways to answer a research question, each of them valid[119]. In this way it "advocates methodological pluralism" in the same way that pragmatism does[122]. As will be discussed in the details of the conceptual framework for this study, these paradigms, and the flexibility they provide in terms of appropriate methods, lend themselves well to the mixed method design utilised within this thesis.

2.2 CONCEPTUAL FRAMEWORK

One of the projects within this thesis aims to explore the feasibility of conducting an RCT to test the efficacy of a short-term fast for reducing treatment toxicities in people receiving Capecitabine and Oxaliplatin chemotherapy (CAPOX) for colorectal cancer (Chapter 4). The potential for fasting to protect against treatment toxicities is based on the concept of starvation-induced differential stress resistance (DSR) which was outlined in Chapter 1 (section 1.3.5). In brief, the theory behind DSR postulates that fasting induces a protective state in non-cancer cells in order

to conserve energy when nutrients are scarce, a process which is mediated by a reduction in IGFs and glucose. Meanwhile, oncogenic changes in cancer cells limit their ability to alter cell signalling processes to divert energy from growth and maintenance to protection and repair, therefore averting the protective effect induced by fasting[42]. This is the pervading concept applied to the studies of fasting in combination with cancer treatment, however the mechanisms behind the concept are not yet well understood. Furthermore, the effectiveness (or otherwise) of DSR in human populations has not been confirmed.

Initiating DSR through short-term fasting could lead to metabolic changes at the cellular level that can be measured and compared to those of a control group of non-fasted subjects within an RCT. However, it is not yet clear from previous research how long participants need to fast in order to induce changes which may offer protection to healthy cells. The length of the fast that people receiving treatment can adhere to is also unclear. To date, studies have not included people with colorectal cancer, and a formative body of work to assess the feasibility of conducting an RCT of short-term fasting in this population is warranted.

The conceptual framework for this body of work supports methods which include both deductive and inductive approaches to answer the question of feasibility of an RCT of short-term fasting during chemotherapy for colorectal cancer. This ties in with the philosophical assumptions entrenched within the pragmatic research paradigm. Stemming from the work on DSR, the conceptual framework for the thesis is rooted in a mechanistic theory, i.e., that short-term fasting induces DSR which in turn may reduce chemotherapy toxicities. This thesis focuses on exploring the feasibility of testing the efficacy of DSR in a future definitive RCT.

There is also a behavioural element to this intervention, as participants will be required to alter their diet through fasting, albeit in the short term, to potentially induce DSR. As such, health behaviour theories may also be useful for informing the design of any definitive RCTs that are developed[123, 124]. Health behaviour theories are used to identify methods or techniques designed to influence health behaviours. Theory-based behaviour change methods target determinants of health behaviour such as self-efficacy or barrier identification, which are in turn believed to influence behaviour[125]. Examples of health behaviour theories used most often within dietary intervention research in cancer populations includes the Social Cognitive Theory and the Trans-Theoretical Model of Change[123, 126]. Social Cognitive Theory postulates that human behaviour is influenced by personal, environmental and behavioural factors. Key constructs within this model include reinforcement,

self-control and self-efficacy (i.e., a person's confidence in their own ability to alter their behaviour and to persist in that behaviour despite any obstacles or challenges)[127]. The Trans-Theoretical Model postulates that health behaviour change requires progress through six stages of change: precontemplation, contemplation, preparation, action, maintenance, and termination. Decisional balance, self-efficacy, and temptations have been found to influence progress through the stages[128].

Interventions informed by theory have been shown to be more effective at inciting behaviour change than those not informed by theory[123]. However, reviews of the effect of theory on dietary interventions have found inconsistent results, and the quality of reported studies can be poor[126, 129]. For example, a recent systematic review of behaviour change theory use in dietary interventions identified that nine theory-based intervention studies aimed at improving diet. The interventions were based on one or more of the following behaviour change theories; Health Belief Model, Social Cognitive Theory, Trans-theoretical Model, Health Action Process Approach and Social Determination Theory. The review identified that theory had not been extensively applied to the design, implementation, and evaluation of the interventions[129]. Only one of the identified studies showed a strong application, while seven showed moderate application, and one showed weak application of theory. The review also identified that theory application was not reported with sufficient detail. Poor reporting and application of theory to intervention design and delivery may explain, in part, inconsistencies in the success of behaviour change based interventions on dietary change. The study that was deemed to show a strong application of theory in the systematic review examined the effect of a tailored behavioural intervention on adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, compared to a non-tailored intervention and usual care group[130]. The tailored interventions used a phone-delivered Trans-theoretical Model based intervention which aimed to facilitate movement of the participants through the stages of change identified in the model. At 6 months follow-up, the tailored intervention group had higher levels of adherence than the other groups. The tailored group was also found to advance through the stages of change when compared to the usual care group (56% vs 43%, $p < 0.01$).

These findings suggest that, when sufficiently applied to intervention design, behaviour change theory has the potential to more effectively incite behaviour change. So, identifying appropriate theories for use in DR interventions during cancer treatment is of interest. Therefore, as will be discussed in further detail, a nested qualitative study (chapter 4, section 4.3.10) and a scoping review (chapter 3) will also be used to explore

participant experiences of following the short-term fast; this will give a deeper understanding of the behavioural aspects of fasting within the trial. This may further build on the conceptual framework, creating a theoretical basis for the delivery of any full scale/definitive RCTs.

A further project within this thesis uses data from a study that compared intermittent energy restriction to continuous energy restriction among women undergoing chemotherapy for breast cancer (Chapter 5, the B-AHEAD 2 trial). A mixed method analysis of quantitative behaviour change data and qualitative interview data investigated the experiences of women undergoing each diet. Again, this study makes use of multiple methods, as befits a pragmatic approach, to further understand experiences of energy restriction during chemotherapy. This population is prone to weight gain during treatment, so the energy restricted diets were designed to aid weight loss in women who were overweight/obese and to maintain weight in those who were normal weight. Within the intermittent energy restriction arm, energy intake was restricted to approximately 800-1000 kcal/day for the two days immediately prior to chemotherapy administration. If feasible, using an intermittent energy restriction diet designed to induce weight loss at this time could offer the additional benefit, compared to the continuous energy restricted diet, of increased protection of healthy cells from cancer treatment, through the mechanisms of DSR.

The dietary restriction interventions implemented in this trial required longer-term restriction and adherence than the short-term fast used in the colorectal feasibility RCT, and as such used established behaviour change techniques, such as goal-setting and self-monitoring, to alter dietary behaviour. Understanding how behaviours were altered during the intervention, and how these may differ for intermittent compared to continuous restriction, will help to inform further research into energy restriction during cancer treatment.

Taken together, the conceptual framework for the thesis can be described as being based on the mechanistic theory of DSR, whereby energy restriction may offer protection from toxicities in people undergoing chemotherapy, while also acknowledging the potential importance of behavioural change theory in informing dietary restriction interventions.

2.3 Research Design

The overall research design includes three distinct but related projects. These are:

1. A systematic scoping review of the literature on dietary restriction at the time of cancer treatment (Chapter 3).
2. A Feasibility RCT of short-term fasting prior to chemotherapy in people with colorectal cancer, including a nested qualitative interview study, to explore patient experiences of taking part in the trial. The design of the RCT was informed by both the systematic scoping review and Patient and Public Involvement, conducted during protocol development and detailed in Chapter 4.
3. A mixed methods analysis of behavioural change and participant interview data, collected during the B-AHEAD 2 RCT of intermittent energy restriction compared to continuous energy restriction, in women receiving chemotherapy for breast cancer (Chapter 5).

Figure 2-1 outlines how these projects are framed within the thesis.

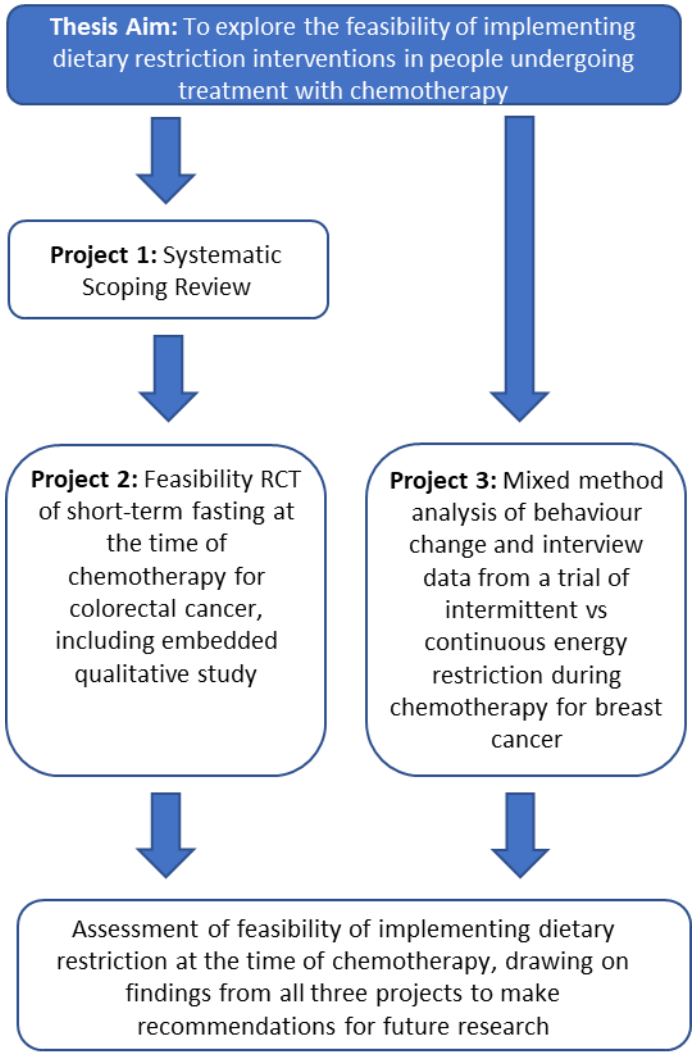

Figure 2-1 Project outline

2.3.1 Systematic scoping review

The literature review for this thesis used a scoping review methodology. A scoping review includes a broader range of evidence than a systematic review and meta-analysis and provides a description of current evidence, regardless of quality[131]. For example, scoping reviews can include case studies as well as RCTs, which form the base of traditional systematic reviews. This allows research in emerging fields, such as dietary restriction during treatment for cancer, which may not yet have results from many RCTs, to be presented and summarised in a systematic way. Scoping reviews can be defined as a way to systematically search for, select and synthesise the knowledge base for exploratory research questions, to help identify the types of evidence that exist as well as gaps in the research for that topic[131].

As previously discussed in Chapter 1 (section 1.4), much of the research on dietary restriction with cancer treatment to date has been completed in pre-clinical settings. As such, a comprehensive systematic scoping review to identify studies in humans looking at the different types of dietary restriction at the time of cancer treatment was warranted.

2.3.2 Feasibility research

Feasibility trials are conducted in order to prepare for and inform future definitive RCTs, where there is some uncertainty about the feasibility of the future RCT[132]. They can also help to reduce waste in research by allowing for modification in the design or conduct of interventions prior to embarking on a large scale study[133]. Due to the paucity of research data on energy restriction during chemotherapy, and some of the potential issues with adherence to and tolerability of dietary restriction interventions, feasibility research is required.

In addition to this, the nature of dietary restriction interventions means they can be considered to be complex interventions. Complex interventions are defined as interventions which have several interacting components and can pose problems for researchers in relation to issues with standardising delivery of the interventions and understanding/measuring complex causal chains that link the intervention and outcome[134]. Dietary interventions, in general, can be considered complex due to the requirement for behavioural change. For dietary restriction interventions in relation to DSR, there is the additional complexity of the multiple underlying mechanisms linked to metabolic

changes. As discussed in chapter 1, the underlying mechanisms behind DSR are not fully understood, and many factors may be involved. The potential for treatment to impact or negate some of the desired metabolic changes that are trying to be achieved through dietary restriction, along with the paucity of data from clinical trials, means that the links between intervention and outcomes are currently unclear.

The Medical Research Council (MRC) has published a framework for developing and evaluating complex interventions, which was updated in 2001[134]. One of the key elements of developing and evaluating complex interventions within this framework is the feasibility/piloting of studies, in order to test procedures for acceptability, estimate recruitment and retention and to determine sample size. The MRC framework also acknowledges that a mixture of quantitative and qualitative methods are often required in order to identify barriers to participation as well as estimating response rates and sample size calculations. Common aspects of trial implementation that require formative groundwork are recruitment and adherence and these are discussed in relation to dietary intervention trials in sections 2.3.2.1 and 2.3.2.2, below. Within this thesis, in order to ameliorate any potential issues with recruitment and adherence to the short-term fasting RCT, a feasibility design was chosen. Lessons learned from this feasibility study can be used to inform full scale trials of this intervention, with the aim of optimising recruitment and adherence. Within the analysis of data from the previous trial of energy restriction during chemotherapy for breast cancer, the analysis focused on understanding behaviour change during the interventions and identifying barriers and facilitators to following the diets, to understand adherence and inform future interventions.

Another step included in the MRC framework for complex intervention is evaluating the intervention[134]. Within this thesis, qualitative research takes on an evaluative role, as discussed in section 2.3.3.1.1 below. Though evaluation in definitive trials will aim to assess effectiveness of interventions, during the feasibility stage it can be used to understand variations in adherence and acceptability of interventions, which may limit the feasibility of interventions. This information can then be fed back into future iterations of the research design/implementation.

2.3.2.1 Recruitment to trials of dietary restriction

Poor recruitment is a common issue in trials. Analysis of National Institute for Health Research Health Technology Assessment funded RCTs reported between 2006 and 2016 found that the final recruitment target size was achieved in only 56% of trials[135]. For the proposed trial of short-term fasting during chemotherapy for colorectal cancer, it is therefore important to consider the potential issues regarding recruitment to

such a trial. Problems with recruitment can lead to a reduction in the power of an RCT due to small percentages of eligible participants consenting to take part[136]. This in turn leads to a need for additional resources to ensure adequate power is reached. Low recruitment rates can also reduce the external validity or generalisability of trial results, if they lead to differences between the trial sample and overall population characteristics, particularly if these differences would affect the risks and benefits of treatment [137].

Many potential issues to recruiting to a trial of fasting may exist. For example, potentially eligible participants may not want to take part due to disliking the concept of randomisation, or having a preference over taking part in either the intervention or control arm[138]. The intervention arm could be viewed as too difficult or the control may be perceived as being the less effective option as it includes no active changes to diet[139] and thus threaten both recruitment to the trial and/or adherence to the assigned intervention arm. Issues can also arise if the intervention being tested is not deemed acceptable by the target population, or if eligibility criteria lead to a reduced eligible participant pool. Feasibility trials are able to highlight any such potential issues with recruitment so that they can be addressed prior to any full-scale trials[133].

2.3.2.2 Adherence to dietary restriction interventions

For both the proposed trial of short-term fasting and the previous trial of intermittent energy restriction, understanding the issues that may impact adherence to the interventions will help to further our understanding of the feasibility of these interventions.

Protocol adherence within an RCT is defined as the degree to which research participants act in accordance with their randomly assigned trial arm instructions[140]. To a greater extent than trials of pharmacological interventions, dietary interventions are embedded in complex cultural and social contexts and rely on participants modifying an existing behaviour, rather than implementing a new one[141]. For these reasons, several barriers to adherence to dietary change may exist. Self-efficacy, is one example, where participants may not have the belief that they are able to make the dietary change required[142]. Perceived social support may also play a role, with dietary change more likely with family or peer support[143]. This is important within the clinical trial setting, because poor adherence will reduce the validity of a trial as it can lead to an underestimation of the treatment effect[144]. Feasibility work can therefore be used to identify some of these barriers to adherence, and also identify factors that may facilitate adherence.

As well as issues with adherence in the intervention arm, methodological rigour could be threatened by poor adherence within the control arm, for example, if they are also motivated to change their diet as per the intervention arm if they feel this may reduce their toxicities[145].

Identifying the factors that affect adherence, through feasibility work, will allow future research to mitigate these issues and therefore reduce the potential for poor adherence to impact trial results.

2.3.3 As dietary interventions are considered complex and require behavioural change in order for efficacy to be assessed, an understanding of the acceptability of interventions is important and requires the utilisation of mixed methods to assess adherence both in terms of acceptability and dietary change. Mixed methods research

Mixed methods research is often linked to the pragmatic research paradigm, as it integrates both quantitative and qualitative techniques and methods, with the aim of utilising the strengths of both methods to address the research question[120, 146, 147]. As described in section 2.3.2 above, mixed methods research also lends itself to the study of complex interventions[134]. The fundamental principle of mixed methods research is that researchers collect multiple forms of data by using different collection methods. This allows the researchers to collect a variety of complementary data, allowing for the development of a deeper understanding of the phenomenon being studied than either method would alone [118, 148].

Traditionally, quantitative research focuses on deductive research, where theories and hypotheses are tested. It therefore lends itself well to the study of reductive phenomena which can be measured, recorded and compared[148]. Qualitative research uses a more inductive and exploratory approach which is useful in the study of more holistic phenomena such as experience, attitudes and opinions. Mixed methods can make use of both induction and deduction[148], making it suited to assessing factors related to feasibility.

Two aspects of how the different research elements are combined must be considered in the design of mixed methods research. The first is whether one method is dominant over the other[148]. The second is the timing of the two elements[148]. In mixed methods designs, the research components can take place either concurrently, where they are conducted at the same time, or sequentially, where one precedes the other[149].

Two elements of this thesis implemented mixed methods design. These were i) the feasibility RCT of short-term fasting during chemotherapy for colorectal cancer and ii) the secondary data analysis from a trial comparing intermittent energy restriction to continuous energy restriction during chemotherapy for breast cancer. Both projects used different designs, as described in section 2.3.3.1 below, to draw on the strengths of mixed methods research, aiming to provide an in-depth understanding of the feasibility of implementing dietary restriction interventions in people undergoing chemotherapy.

2.3.3.1 Mixed methods in a feasibility RCT of short-term fasting at the time of chemotherapy for colorectal cancer (Chapter 4)

2.3.3.1.1 Rationale

If conducting a trial of the effect of fasting on chemotherapy toxicities, we would be interested in the potential effects of short-term fasting on the research participant. These effects could be measured quantitively by recording outcomes such as blood sample analyses and patient surveys, and the results compared statistically, in order to test efficacy of the intervention in a definitive trial. Therefore, within this current feasibility research project, quantitative methods are appropriate for studying the measures that would constitute the main primary outcomes of a definitive RCT, such as biomarkers of effect and adverse event statistics. As per the MRC framework, this allows the feasibility research to provide initial data for estimating response rates and sample size calculations. Similarly, the primary feasibility outcomes such as number of participants recruited, and number of withdrawals can be recorded and described quantitatively. However, trials of dietary interventions also require participants to modify their behaviour. In this feasibility study, participants randomised to the fasting arm are asked not to consume any food while on the short-term fast. To assess the feasibility of the trial, participant experience of making this dietary change and whether they were able to alter their diet as per the trial protocol, is also of interest. The aim of this aspect of the feasibility study is to develop a trial that can be implemented in the clinical group being recruited and identify whether uptake and adherence could be optimised for a definitive RCT. In this way, diet can be viewed as both a reductive and holistic phenomenon. On the one hand, it requires the intake, or absence in this case, of food. This can be monitored, recorded and the effects on various biological outcomes measured and analysed by statistical methods. Conversely, altering diet is a health behaviour which is affected by varying factors including participant's experience of the fast and its side effects, their attitudes towards the diet and social or practical barriers to taking up the fast. Using a mixed method design within this feasibility research

allows for the exploration of different facets of the response to the intervention[150] and extends our understanding through using multiple perspectives to assess the research question[147]. Thus, one purpose of using mixed methods is for complementarity, where the qualitative methods will be used to elaborate and enhance the findings from the quantitative methods[150].

Similarly, while the quantitative element of the feasibility RCT measures the number of recruits and the levels of adherence overall, the qualitative element of the trial will appraise how it was experienced and what might make the fasting protocol easier to follow. In this way the function of the qualitative research is also evaluative in nature[147]. Overall, it will allow for a deeper understanding of the context in which the fasting intervention occurred, helping identify any barriers or enablers to following the fast, therefore helping inform future research. This aspect of the intervention has not been fully explored in previous trials of fasting, so it is unclear which concepts from health behaviour theories would be most useful for informing short-term fasting interventions. Therefore, the qualitative component of this project takes on an evaluative and complementary role, providing further information on the experiences of fasting and taking part in the trial. The presiding method is therefore quantitative, with qualitative methods supplementing the quantitative results.

2.3.3.1.2 Design

The quantitative (quant) and qualitative (qual) aspects of the feasibility RCT of short-term fasting were combined in a mixed methods research design and were conducted following the steps outlined in the mixed methods research process model[148]. This model is comprised of 8 different steps which are to:

1. determine the research question
2. determine whether a mixed design is appropriate
3. select the mixed method or mixed-model research design
4. collect the data
5. analyse the data
6. interpret the data
7. validate or legitimise the data

8. draw conclusions (if warranted) and write the final report

A schematic of this model and how it was applied to the research question is outlined in Figure 2-2. Step 1, identifying the research question, was outlined in chapter 1. Steps 2 and 3 are discussed in further detail in this section below, while the methods used in steps 4 to 8 are

described in detail in Chapter 4 of the thesis.

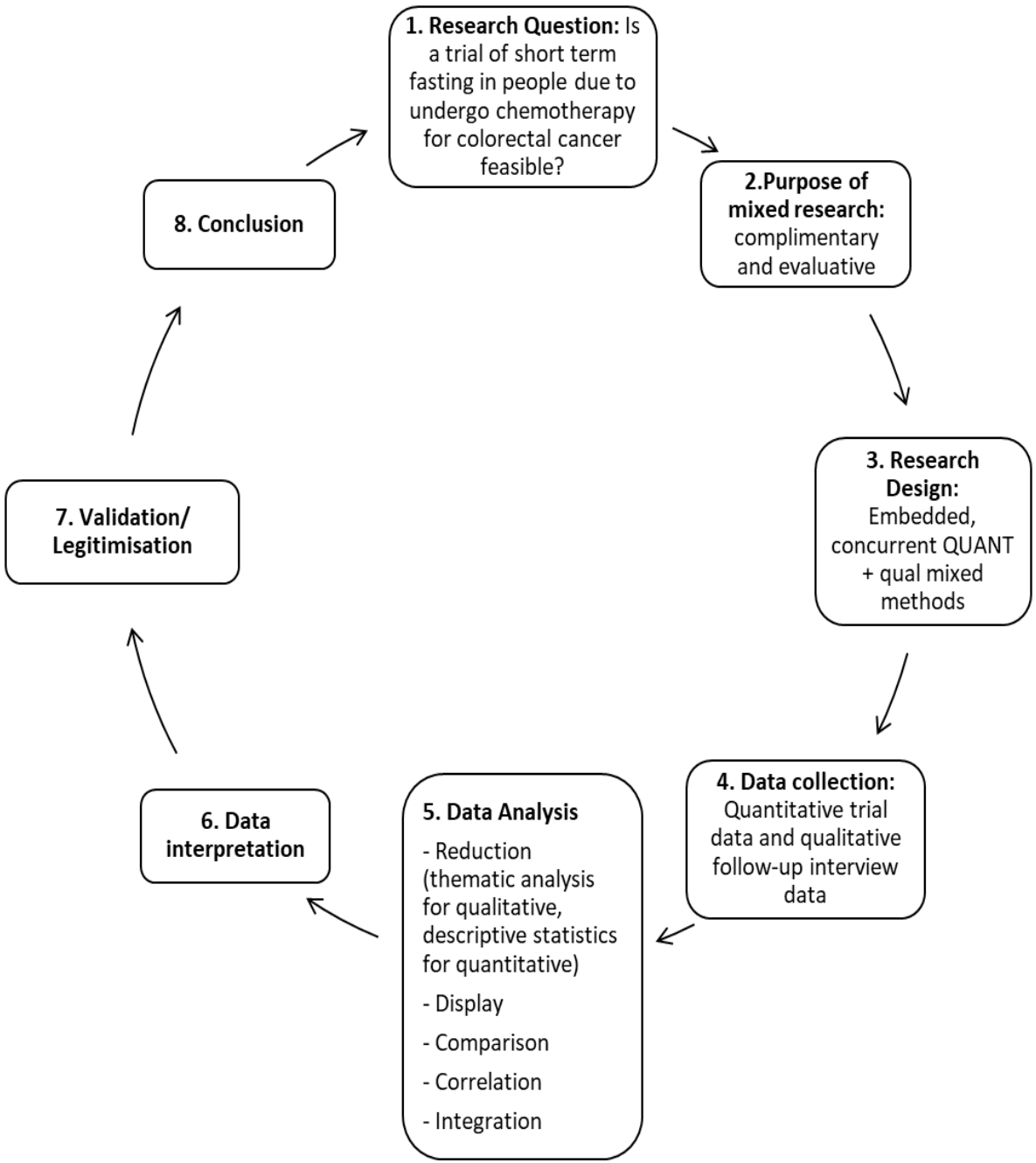
1. Research Question: Is a trial of short term fasting in people due to undergo chemotherapy for colorectal cancer feasible?
2.Purpose of mixed research: complimentary and evaluative
3. Research Design: Embedded, concurrent QUANT + qual mixed methods
4. Data collection: Quantitative trial data and qualitative follow-up interview data
5. Data Analysis
- Reduction (thematic analysis for qualitative, descriptive statistics for quantitative)
- Display
- Comparison
- Correlation
- Integration
6. Data interpretation
7. Validation/ Legitimisation
8. Conclusion

Figure 2-2 – Research process model, adapted from Johnson et al, 2004[148], where QUANT is capitalised as the presiding method

The purpose of using a mixed methods design is to provide complimentary data on the feasibility of the intervention. Whereby the quantitative methods will be used to provide data on outcomes of interest, recruitment and adherence, while the qualitative methods will be used to elaborate and enhance the findings from the quantitative methods, by providing more in-depth understanding of acceptability and tolerability.

This Embedded Concurrent Mixed Methods design is summarised in the diagram below (figure 2-3), where “quan” is capitalised as it is the dominant research domain. Within the feasibility RCT, the two components take place almost simultaneously. As will be discussed further in chapter 4 section 4.3.10, the qualitative interviews are conducted once participants complete their final chemotherapy cycle of the trial. Conducting the interviews throughout the feasibility trial will allow for any informative evaluative findings to be fed back into the trial design, updating the intervention delivery for subsequent participants, if required. Here, the qualitative component of this project takes on an evaluative and complementary role, providing further information on the experiences of fasting and taking part in the trial.

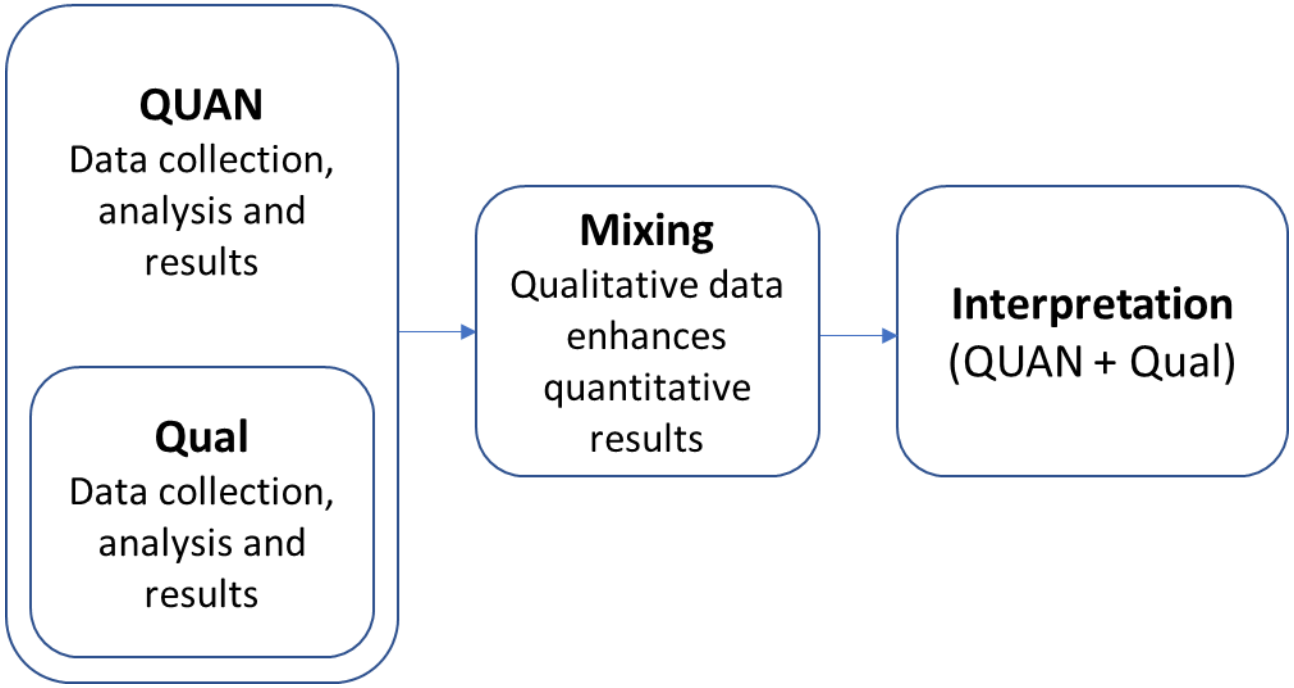

Figure 2-3: The Embedded Concurrent Mixed Methods Research Design, adapted from Creswell et al, 2006[151].

2.3.3.2 Mixed methods analysis of behavioural change and interview data in women receiving chemotherapy for breast cancer (Chapter 5)

2.3.3.2.1 Rationale

Within the B-AHEAD 2 trial (chapter 5), quantitative behaviour change data were collected to assess the behavioural and psychological factors which motivate or reduce adherence to the two diets used in the trial. Qualitative interview data were also collected to further explore participant experience of adherence, providing more in-depth data on the potential barriers to and facilitators of adherence. In this way the quantitative and qualitative data were used in combination, using the strengths of each to allow for a more in-depth analysis of the issues surrounding feasibility of dietary restriction during chemotherapy[152].

2.3.3.2.2 Design

The concurrent triangulation design involves the concurrent, but separate, collection and analysis of quantitative and qualitative data in order to answer the research questions (Figure 2-4)[151]. Within the concurrent triangulation design, both methods are implemented during the same timeframe and are also afforded equal weight[151]. Affording both methods equal weight within this analysis allows the strengths of both to be utilised to provide a more in-depth understanding of the factors which affect adherence to intermittent energy restriction, and how this may differ to continuous energy restriction. Ultimately, the aim of providing this more in-depth knowledge, is to help to inform future interventions of energy restrictive diets during cancer treatment. Triangulation, within mixed methods research refers to the process of using different methods to gain a more complete picture of the topic being addressed by the research. It involves outlining where findings from each method converge, offers complementary information and highlights any discrepancies between the data[153]. Integrating the results of both the quantitative and qualitative analyses in this way allows for a more in depth interpretative narrative of the results[154].

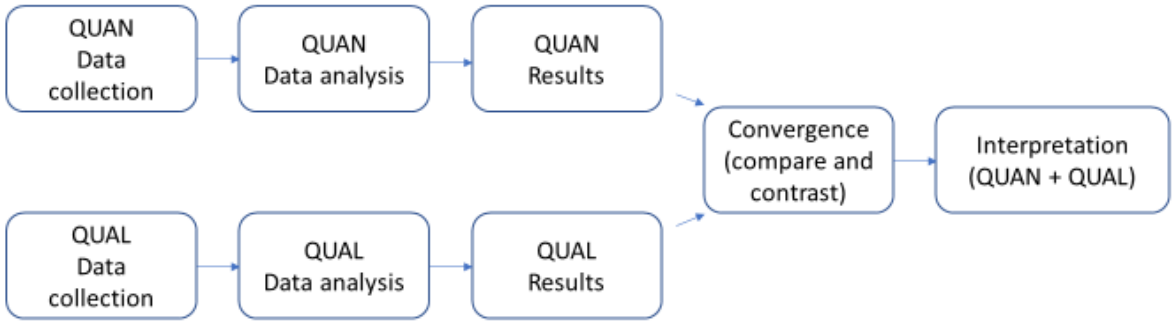

Figure 2-4 - Concurrent Triangulation Design (Convergence Mode), adapted from Creswell et al, 2006[151].

For the analysis of the B-AHEAD 2 data, the quantitative and qualitative components of the trial were integrated at the interpretative/reporting stage of the analysis[155]. In this way the convergence model of triangulation was followed. The quantitative and qualitative data were analysed separately as described above for both components. Results from each component were then converged during the interpretation stage by comparing and contrasting the results, using the data triangulation method[151, 156].

2.4 SUMMARY

This body of work was grounded in two philosophical paradigms. The post-positivist approach allowed for the scientific rigour of more traditional positivist research to be followed, while allowing for the interpretive nature of studying research phenomenon such as participant experiences. The research was also pragmatic in nature, allowing the focus of the methodological choices to be based upon how best to answer the research question, rather than on any one method alone.

The conceptual framework drew on the existing concept of fasting induced DSR during cancer treatment. It aimed to produce formative research into the feasibility of testing this theory in suitably powered RCTs of dietary restriction during chemotherapy. It also acknowledged the potential importance of behaviour change theory in some intervention designs, and aimed to explore, through qualitative analysis and review of the literature, whether more can be done to ground future research in health behaviour theories which may improve uptake and adherence to dietary restriction interventions.

This body of work focused on feasibility research in order to explore potential issues related to trial recruitment and adherence to dietary restriction interventions. This allows any issues identified to be mitigated, where possible, in future research of interventions of dietary restriction during chemotherapy.

Mixed methods designs were utilised in two projects within this thesis. This is a useful design for studying the intervention from both a reductive and holistic point of view. For the proposed RCT of short-term fasting in people receiving chemotherapy for colorectal cancer, quantitative methods are used to capture the feasibility outcomes as well as the secondary outcomes that may form the primary outcomes in a definitive RCT. Qualitative methods are used to evaluate the ability of participants to take part in the trial, and their experiences of it. For the analysis of behaviour change and interview data in a trial of intermittent or continuous energy restriction in people receiving chemotherapy for breast cancer, quantitative behaviour change data and qualitative interview data are interpreted concurrently, to allow for an in-depth understanding of participant experiences of adhering to the intervention.

The data collection methods used within each project that make up this body of work will be discussed further in the following thesis chapters.

Key Messages

1. This thesis is anchored in two complementary research paradigms: post-positivism and pragmatism.
2. The conceptual framework is based on the concept of DSR, which is described in detail in Chapter 1, while also acknowledging the potential importance of behaviour change theory in guiding interventions.

3. Due to the paucity of data on dietary restriction during treatment of cancer, this body of work focuses on exploring the feasibility of implementing these interventions at the time of chemotherapy, with a particular focus on recruitment and adherence data.
4. Employing mixed method designs within this thesis allows for a variety of complementary data to be collected and analysed, to explore the feasibility of implementing interventions of dietary restriction in an holistic manner.

Chapter 3 SYSTEMATIC SCOPING REVIEW

This systematic scoping review comprised the first project within the thesis on dietary restriction during cancer treatment. It was used to synthesise the research to date on dietary restriction as an intervention to reduce cancer treatment toxicities. Synthesising the current literature allowed this review to inform the development of the protocol for testing the feasibility of a fasting intervention in people with colorectal cancer which is detailed in chapter 4.

The systematic scoping review has been published as a research article in the journal BMC Cancer[1]. This chapter details the background (section 3.1), methods (section 3.2) and results (section 3.3) of the published review.. Due to this, there is some overlap with the content of section 1.3.5 of the background chapter in this thesis. In an addendum to the published version of the review, this chapter also provides the summary of an updated search which was conducted after publication, and also outlines the implications of the results for the thesis as a whole. The scoping review protocol was developed and led by ES with input from RP and review by CA, CP, GH and AN. The search criteria were developed by ES with database specific support from RP. ES screened all of the abstracts. Abstracts were also second screened by one other researcher (RP, CA, AM and CE). ES, RP, and CA extracted the data. The results and interpretation were written by ES and reviewed by RP, CA, AM, CP, GH and AN.

3.1 BACKGROUND

Pre-clinical studies in model organisms have identified the potential protective effect of restricting overall energy intake or specific macronutrient intake on resistance to stress in these models. This has led to a growing interest in the use of restrictive diets to potentially attenuate the cytotoxic effects of cancer treatments such as chemotherapy and radiotherapy[59]. Examples of diets of interest include fasting, which restricts overall energy intake, and ketogenic diets, which restrict energy intake from carbohydrate sources. Collectively these diets can be referred to as dietary restriction (DR)[57].

3.1.1 Using dietary restriction to induce Differential Stress Resistance

When nutrients are not available, non-tumour cells are able to alter their cell signalling processes, withdrawing energy from growth/reproduction to conserve their energy for maintenance/repair. This leads to increased cellular protection[44]. This process is partially mediated by a reduction in glucose

and growth factors, specifically insulin-like growth factor-1 (IGF-1)[6]. A reduction in IGF-1 reduces the activation of the Ras/MAPK and P13K/Akt signalling pathways that promote expression of genes involved in proliferation, growth, survival, and increased protein synthesis via mTOR.

Conversely, cancer is a disease associated with dysregulated metabolism[41]. One of the hallmarks of cancer is the ability of tumour cells to continue to grow in the absence of growth factors, such as when nutrients are scarce[7]. Mutated tumour cells evade these signals due to gain-of-function mutations in oncogenes (Ras, Akt, mTOR), which results in proliferation pathways continually being active, even in the absence of growth signals[44]. Therefore, tumour cells do not respond to nutrient deprivation in the same way as healthy cells and continue to proliferate, even when nutrients are scarce. The Warburg effect also stipulates that tumour cells use glycolysis, rather than oxidative phosphorylation for energy production [48, 50, 51], potentially putting tumour cells under increased pressure when cells are required to switch from glucose metabolism to ketone metabolism and fatty acid oxidation if glucose supplies are low[53].

This difference in reaction to nutrient scarcity between healthy and tumour cells is termed differential stress resistance (DSR) and may render tumour cells more susceptible to the effects of chemotherapy while at the same time helping to protect healthy cells against the toxic effect of treatment[59]. It is thought that through mechanisms such as decreased growth signalling for healthy cells and the lack of metabolic adaptability found in tumour cells, DR may lead to the increased vulnerability of tumour cells to treatment. Therapeutic regimes that take advantage of DSR are therefore a potential tool in the treatment of cancer.

Methods of DR such as fasting, carbohydrate restriction or protein restriction are dietary strategies which aim to exploit this difference in energy metabolism between healthy and tumour cells[66].

Chronic energy restriction and fasting lead to reduced blood glucose and IGF-1 and increased ketones[96]. However, chronic energy restriction may not be suitable for patients undergoing treatment with chemotherapy or radiotherapy due to the increased risk of cachexia and sarcopenia [44, 53]. Short term fasting (for example complete energy restriction lasting up to 4 days) at the time of chemotherapy has therefore been suggested as a potential therapy without the risks of chronic energy restriction[57]. More recently, a fasting mimicking diet has been created that mimics the physiological effect of fasting without having to reduce daily energy intake below 725kcal. This diet aims to overcome some of the

difficulties of short term, water only fasting, such as adherence, adverse effects and malnourishment[96].

As well as energy restriction, the composition of restricted diets may also be of importance. Ketogenic diets (KDs) are high in fat with restricted carbohydrate intake. For example, the 4:1 KD comprises fats in a 4:1 ratio to carbohydrates, whilst also limiting protein intake, so that approximately 90% of energy is derived from fat[157]. KDs simulate many of the physiological responses of energy restriction such as a reduction in blood glucose and IGF-1 coupled with an increase in ketones [53, 66].

Protein restriction is another form of macronutrient restriction that is potentially relevant. Epidemiological research has found that people following energy unrestricted plant-based diets, with reduced protein, have lower IGF-1 concentrations than those on long-term severe energy restriction with adequate protein [72]. Protein restricted diets aim to reduce intake of total protein or of specific essential amino acids. Methionine (MET) is of particular interest, as an amino acid that has been recognised to have an important role in cellular metabolism. It is required for protein synthesis and DNA methylation required in cell growth/proliferation[105].

3.1.2 Previous Reviews

Reviews on DR that have been published to date have focused on subsets of DR studies and not all have been systematic in their search criteria. Previous systematic reviews have been conducted in fasting[62] and KDs[104] and are described below.

As discussed in section 1.4.2, the review of fasting included studies on the effects of chemotherapy and studies on tumour progression, without chemotherapy. This review focused primarily on the findings from animal research although it included three human studies conducted in the USA[158, 159] and the Netherlands[160] that were published between 2009 and 2015. These were; a case series report of 10 cases with various malignancies who had voluntarily fasted during chemotherapy treatment[158], a dose-escalation study in 20 participants receiving platinum-based combination chemotherapy for various malignancies[159], and a pilot RCT in 13 women receiving chemotherapy for HER2-negative, stage II/III breast cancer[160]. The case series report of people who chose to fast voluntarily reported a broad range in length of fasts followed (48-140 hours prior to chemotherapy and/or 5-56hrs following chemotherapy). The interventional studies also used a variety of fasting durations. The dose escalation study included three cohorts which fasted for 24, 48 and 72 hours. The 24 and 48 hour fasts were followed prior to chemotherapy, while the 72 hour fast was divided as 48 hours prior to and 24 hours

post-chemotherapy. Results from the individual studies included in the review are detailed in 3.3.1.3 of this review. Authors of the systematic review concluded, from both the pre-clinical and human studies, that fasting appeared to reduce chemotherapy side effects and suppress tumour progression. They also concluded that a 24hr fast may not be long enough for the protective effects of fasting to apply. This was because two human studies found less toxicities in 72hr fasts when compared to 24hr fasts[17, 18].

The review of KDs was not conducted specifically in populations receiving active treatment for cancer[104]. It included adult patients following a KD as a complementary therapy prior to, alongside or after standard anticancer treatment, for more than 7 days. The review identified 11 studies, all early-phase trials (n=3), cohort studies (n=3), case reports (n=4) and one retrospective review, which included a total sample of 102 participants (age range 34–87 years). The majority of studies involved participants with brain cancer (n=5), one involved participants with rectal cancer, while the remaining five studies included participants with mixed cancer sites. The studies varied in terms of both the duration and type of KD. The duration of KDs ranged from 2.4 to 134.7 weeks. While the ratio of fat to carbohydrate and protein ranged from 4:1 or 3:1 in three studies, 0.7:1 and 1.8:1 in two studies and 2:1 in one study. Three studies used a modified Atkins diet which, rather than provide a ration of fat to carbohydrate/protein, allowed participants to consume on 20-40g carbohydrate/day. Overall, the authors reported inconclusive evidence for changes in nutritional status and adverse events as well as low adherence to KDs, as only 49% of participants were able to complete the diet, overall. The studies that were used alongside cancer treatment were included in this current review and the results are provided in section 3.3.1.1.

No systematic reviews have been conducted on other forms of DR during treatment for cancer e.g. fasting mimicking diets or protein restriction.

In addition to the systematic reviews, two perspective reviews describing the rationale behind fasting and fasting mimetics at the time of chemotherapy have also been identified [44, 53]. These reviews describe how the findings in simple organism and animal models provide a rationale behind the use of some forms of DR and provide an overview of previous[44] and ongoing [53] DR trials. The first review by Lee and Longo, 2011, references the pre-clinical research in DSR, ranging from initial studies in yeast which found that starvation promotes protection against oxidative stress and increases life span, to more recent studies in mice which found that fasting for 48–60 h increases protection from oxidative stress and improves survival in mice treated with the drug etoposide compared with mice fed *ad libitum*. The authors use this preclinical research to describe the proposed mechanisms by which starvation may

lead to cellular stress resistance and discuss how IGF-I signalling pathways mediate this increased resistance, as described in section 1.3. The second perspective review by O'Flanagan, 2017, also summarises the pre-clinical findings from studies of energy restriction and the biological mechanisms underlying DSR. However, this review describes a broader range of potential diets, including KDs and the intermittent, 5-2 diet, that may also induce DSR. This perspective review also provides a summary of clinical trials (both completed and ongoing) that include energy restriction diets or energy restriction mimetic drugs, in combination with chemotherapy or radiotherapy. It identified four planned/ongoing trials of fasting, one of FMD and five of KDs. Although both perspective reviews provide a useful overview of the research in DR and describe the proposed biological mechanisms behind DSR, they do not describe a systematic search of the literature, and additional studies on DR in humans, not included in these reviews, have been identified.

3.1.3 Aims and objectives

The aim of this scoping review is to summarise the research on the effects of DR on cancer treatment induced toxicities and outcomes in adults undergoing treatment for any malignancy. Although previous reviews have focused largely on DR alongside chemotherapy, the mechanisms behind DSR have the potential to offer protection to non-tumour cells against other forms of treatment, such as radiotherapy and tyrosine-kinase inhibitors[65, 161]. Furthermore, as well as mechanistic factors, it is possible there may be some commonalities in, for example, barriers to recruitment or following particular diets, across different cancer treatments, which could be used to inform future studies of DR. As such, the opportunity was taken to summarise the research on DR alongside all forms of cancer treatment rather than focusing on chemotherapy alone.

The primary objective is to identify and characterise the research that has been conducted to date on DR as an adjuvant therapy in the treatment of cancer in adults with cancer. The secondary objective is to explore the acceptability of dietary restrictions in the samples identified through the search.

3.2 METHODS

A scoping review protocol was developed and made publicly available prior to commencement of this review[162].

3.2.1 Inclusion Criteria

Inclusion criteria were defined in terms of Population, Concept and Context[163].

Population – Adult participants undergoing some form of DR as an adjuvant treatment for any type of cancer.

Concept – Any form of DR studies which assessed:

i) The safety or feasibility of the interventions and/or

ii) The effect of the interventions on outcomes such as chemotherapy toxicities, clinical outcomes or cancer biomarkers. Examples of the forms of DR of interest are short/long term fasts, intermittent fasts, fasting mimicking diets, KDs or protein restriction diets.

Context – Any cancer care setting. The intervention could be delivered in combination with any standard treatment for cancer e.g. chemotherapy, radiotherapy or immunotherapy.

3.2.2 Exclusion Criteria

Studies of animal models or model organisms were not included in this review. Although not specified in our original protocol, as we were interested in diets that result in the metabolic changes associated with DSR and not diets that altered macronutrient composition without aiming to induce such changes, low fat diets which solely aimed to reduce weight in cancer populations were also excluded.

3.2.3 Types of sources

All forms of quantitative and qualitative primary research were included, as were systematic reviews and meta-analyses. As DR is an emerging field, observational studies, case reports and conference abstracts were included in addition to trials. There were no limitations on date or language of publication.

3.2.4 Search Strategy

The following databases were searched for relevant articles on the 4th January 2018:

1. MEDLINE, Embase, AMED (via OVID)
2. CINAHL
3. Web of Science

The coding for the search strategy was developed by the lead researcher (ES), with input and advice from a systematic reviewer (RP) and was based on the inclusion criteria. An example of the search strategy used in MEDLINE is shown in Appendix A. The search terms were updated for each database (by RP), in accordance with their specific requirements.

In addition to the database searches, the reference lists of all included articles were hand searched by ES for additional studies alongside relevant systematic reviews. The ClinicalTrials.gov website was searched to identify any trials currently taking place which have not yet been completed or published. As an addition to the original protocol, the International Standard Randomised Controlled Trial Number registry (ISRCTN) database was also searched for planned or ongoing trials. Finally, the first ten pages of google scholar were hand searched for any additional articles.

The results from the database searches were imported into an Endnote library and duplicates were removed during the data screening process.

3.2.5 Selection of studies

Titles and abstracts of the search results were screened independently by two reviewers from a team of five researchers. Any discrepancies were discussed with a third reviewer for resolution, if required. Articles identified for potential inclusion were retrieved in full for further screening against the inclusion/exclusion criteria. These were also screened independently by two reviewers (ES plus a second reviewer from the team of five researchers). Full texts which met the inclusion criteria underwent data extraction.

3.2.6 Data extraction

Data charting forms were used to extract relevant data from the included studies. Charting forms were completed by two reviewers independently (ES plus a second reviewer), then compared for accuracy. Extracted data included:

a) Publication Information – Paper title, author details, publication type, study type, year of study
b) Aims/purpose of the research
c) Study population – Sample size, demographics (age, sex, ethnicity), cancer site and staging, inclusion/exclusion criteria, withdrawals and exclusions
d) Intervention type and design – Study design, intervention description (including type, timing and duration of DR)
e) Key findings – Outcomes reported, outcome measures, adverse events, adherence rates, acceptability and tolerability.

3.3 RESULTS

The inclusion flowchart for the review can be seen in Figure 3-1.

The database search retrieved 8448 texts for screening and 4 additional manuscripts were identified through hand searches. Title/abstract screening identified 84 texts for full text screening. Fifty were excluded, with reasons recorded in Figure 3-1. Thirty-four full texts which described 23 studies in total, were identified for inclusion in the review and underwent data extraction.

3.3.1 Characteristics of included studies

The 23 included studies were published between 2007 and 2017 and included a total sample size of 990 (range 1-596 in the observational studies and range 6-73 in the interventional studies). Four categories of interventions were identified: KDs, fasting, protein restriction and combined interventions. A summary of included study characteristics is outlined in Table 3.1. The majority of studies were of KD (n=10), followed by protein restriction (n=5), fasting (n=4), and combined interventions (n=4). The outcomes reported were varied, ranging from withdrawal rates, treatment side effects (both standard treatment and/or intervention effects) and biological markers. Results were therefore divided into three broad groups of interest: feasibility, tolerability and treatment effects. These results are reported for each intervention category in Tables 3-2 to 3-5 and described in further detail below. Results grouped under “Feasibility” included any recruitment, retention and attrition rates that were reported. Results grouped under “Tolerance” included self-reported measures of tolerability, including acceptability of interventions, and adverse events, including weight loss. Where adverse events were attributed by authors to the dietary intervention, they have been included under “tolerability”. Where they were reported in relation to their treatment e.g., chemotherapy side effects, they are included under “treatment effects”. Any treatment effects reported which could be of interest as main outcomes in large scale RCTs were recorded under “Treatment Effects” and included results for markers of metabolism, treatment related toxicities and quality of life.

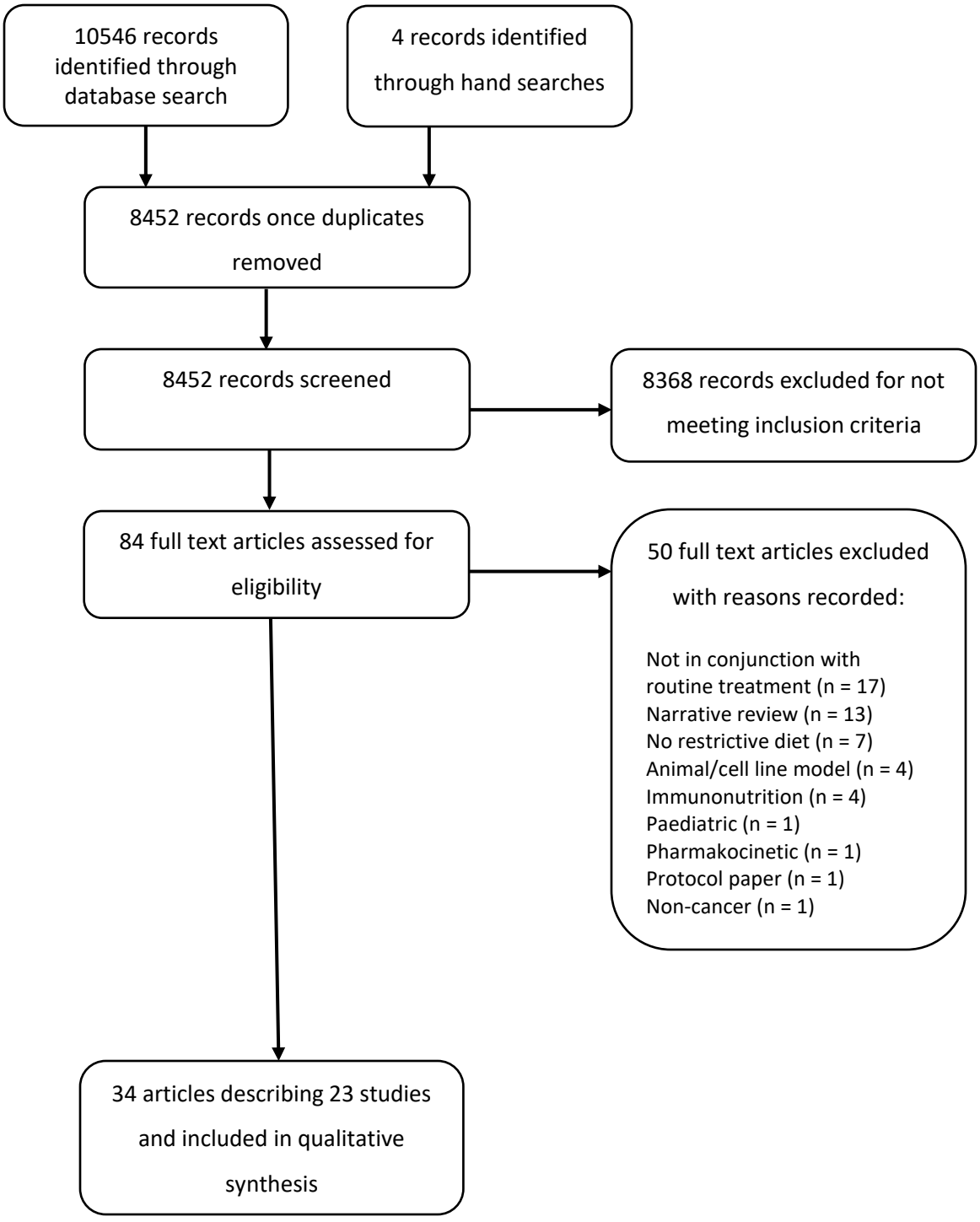

Figure 3-1: Inclusion Flowchart

Table 3-1: Summary of characteristics of included studies

Reference (author, year, country)	**Design**	**Cancer Type**	**No. of Participants**	**DR Intervention**	**Cancer treatment**
Ketogenic Diets					
Cohen, 2016[164], USA	Feasibility RCT	Recurrent ovarian cancer	73 randomised, 45 analysed (25 in IG, 20 in CG)	KD: 5% CHO, 25% protein, 70% fat over 12 wks.	Usual care (24% received concurrent chemotherapy)
Anderson 2016[165] , USA	Phase 1 trial with single assignment	Stage 3-4b head and neck squamous cell carcinoma	9	4:1* KD fed by PEG followed by oral intake for 5 wks.	Concurrent platinum chemo-radiotherapy
Renda 2015 and Dardis, 2017[166], USA	Phase 1/2 trial with single assignment	Brain cancer	14	4:1 KD* for 8 wks during concurrent radiation and chemotherapy, followed by a 1:1 diet	Adjuvant temozolomide chemotherapy
Rieger 2010[167] and Rieger, 2014[168], Germany	Pilot study with single assignment	20	20	KD: <60 g/day CHO consumed with 500ml highly fermented yoghurt drinks and 2 plant oils daily. Followed diet for 6-8 wks alone and for a further 6-8 wks	Either alone or during salvage chemotherapy (n=8)
Zahra, 2017[169], USA	Phase 1 trial with single assignment	Non small cell lung cancer (n=7) Pancreatic cancer (n=2)	9	4:1 KD: 90% fat, 8% protein,2% CHO (KetoCal powder + food provided). KD 2 days prior to chemo-radiotherapy until end of treatment (6wks for lung and 5wks for pancreatic)	chemo-radiotherapy

Reference (author, year, country)	Design	Cancer Type	No. of Participants	DR Intervention	Cancer treatment
Artzi, 2017[170], Israel	Non randomised trial	Brain cancer	9 (5 in IG, 4 in CG)	4:1 KD using KetoCal® formula for 2-31 months	Bevacizumab, temozolomide or rindopepimut
Champ, 2014[171], USA	Retrospective review	Grade 3-4 glioblastoma	53 (6 cases, 47 controls)	"Patient driven KD" – CHO levels below 50g/day or 30g/day if ketosis not reached	Chemo-radiotherapy or adjuvant chemotherapy
Klement, 2016[172], Germany	Case series	Breast (n=1), prostate (n=1), rectal (n=3) and lung (n=1) cancer	6	KD: 80% fat and <50 g/day CHO during treatment (mean 48.2 days, range 32-73 days)	Radiotherapy or chemo-radiotherapy
Attar 2015[173] and 2016[174], USA	Retrospective review	Recurrent brain cancer	13	Modified Atkins Diet: up to 60g/day carbohydrate (2-5% total calories) from 1-21months	Chemotherapy(n=9) or no treatment
Randazzo, 2015[175], USA	Retrospective data registry review	Brain cancer	596 (81 cases, 515 controls)	Self-administered "special diets" including KD, Low CHO, vegetarian/vegan	Usual care
Protein Restriction Diets					
Eitan, 2017[176], USA	RCT	Prostate cancer	38 (19 IG, 19 CG	Protein restricted diet (0.8 g protein kg -1 lean body mass)	Awaiting surgery (43±11 days on diet)

Reference (author, year, country)	Design	Cancer Type	No. of Participants	DR Intervention	Cancer treatment
Durando, 2008[177], France	Phase 1 clinical trial with single allocation	9 metastatic melanoma, 1 recurrent glioma	10	MET-free diet ranging from 1-4 days	4 cycles of cystemustine chemotherapy
Durando, 2010[178], France	Feasibility study with single arm assignment	Metastatic colorectal cancer	11	MET-free diet for 3 days	3 cycles of FOLFOX chemotherapy
Thivat, 2007[179], France	Phase 1 trial with single arm assignment	1 recurrent glioma, 5 metastatic melanoma	6	MET-free diet ranging from 1-4 days	4 cycles of cystemustine chemotherapy
Thivat, 2009[180], France	Phase 2 trial with single arm assignment	20 melanoma, 2 glioma	22	1 day MET-free diet	4 cycles cystemustine chemotherapy
Short Term Fasts					
De Groot 2013[181] and 2015[160], Netherlands	Pilot RCT	Stage 2-3 breast cancer	13 (7 IG, 6 CG)	48 hr fast (24h before until 24h after start of chemotherapy)	3 weekly (neo) adjuvant TAC-chemotherapy
Dorff, 2016[159] and Quinn, 2013[182], USA	Dose escalation	Any cancer	20	3 cohorts fasted before chemotherapy for 24, 48 and 72 h (divided as 48 pre-chemo and 24 post-chemo)	Platinum based chemotherapy
Mas, 2017[183], France	Qualitative	Breast cancer	15	Self-administered fast	Chemotherapy

Reference (author, year, country)	Design	Cancer Type	No. of Participants	DR Intervention	Cancer treatment
Safdie, 2009[158] and 2010[184], USA	Case series	Breast (n=4), prostate (n=2), ovarian (n=1), uterine (n=1), lung (n=1), oesophageal (n=1) cancer	10	Self-administered fast ranging from 48-140 hrs prior to and/or 5-56 hrs	Chemotherapy
Combined Interventions					
Freedland, 2016[185], USA	RCT	Prostate cancer	40 (19 IG, 21 CG)	Low CHO diet (<20 g/day) combined with moderate physical activity increased by 30 min/day for 5 days/wk	Androgen Deprivation Therapy
Reinwald, 2015[186] and Branca, 2015[187], Italy	Case report	Breast cancer	1	An isocaloric KD: special amino acid formula combined with probiotic yoghurt containing vitD binding protein macrophage activating factors and injections of vitD, oleic acid and vitD binding protein	3 weeks prior to surgery
Iyikesici, 2017[188], Turkey	Case report	Triple negative breast cancer	1	12h fast followed by 5-10 units of insulin. Patient also consumed a KD for duration of treatment	Chemotherapy
Zuccoli, 2010[189], Italy	Case report	Brain cancer	1	Self-administered post-operative fast followed by a calorie restricted KD with chemo-radiotherapy. KD: 600ckal/day using Keto-Cal® 4:1 supplemented with multivitamins. After approx. 2 months on restricted KD, patient switched to a	Post-surgery

				calorie restricted non-KD (600kcal/day) for 5 months.	
Abbreviations: CG, Control Group; CHO, Carbohydrate; IG, Intervention Group; KD, Ketogenic diet; MET, Methionine; Ppts, Participants; RCT, Randomised Controlled Trial;					

3.3.1.1 Ketogenic diets

Ten studies of KDs that were conducted alongside treatment for cancer were identified: one randomised controlled trial (RCT)[164], four single arm trials[165-167, 169], one non-randomised, parallel design trial[170] one case control study[171], one case series[172] and two retrospective reviews[174, 175]. Four of the studies also included participants who were not on any active treatment at the time of the DR [164, 167, 174, 175]. However, as they reported on outcomes of interest relevant to our research question (e.g., adherence) they were included in the review. The majority of KD studies were in people with brain cancer (n=6) and the most common form of diet was a 4:1 ratio KD (n=5). The results are summarised in Table 3-2.

Table 3-2: ***Ketogenic Diet Results Table (n=10)***

Reference (author, year, country)	**Design**	**Population** (No. of ppts, age, site/lesion type)	**Intervention** (DR intervention, corresponding cancer treatment)	**Feasibility***	**Tolerance**	**Treatment effect**
Cohen, 2016[164], USA	Feasibility RCT	73randomised, 45 analysed (25 in IG, 20 in CG) Mean age 60.2y (range 31-79y) Recurrent ovarian cancer	KD: 5% CHO, 25% protein, 70% fat over 12 wks. Usual care (24% received concurrent chemotherapy)	40% recruitment rate(73 out of 182 assessed for eligibility) 62% retention 80% adherence (defined as ~0.5 mmol/L urinary ketone conc.)	↔ lean body mass between groups ↓total body fat (kg) (32.7 ± 3.1 vs 41.2 ± 4.4) android fat (kg) (2.8 ± 0.4 vs 3.6 ± 0.5), and visceral fat (g) (975 ± 150.9 vs 1024 ± 175.6) (p<0.05) in IG	↓insulin (μU/mL) in IG (6.7 ± 0.9 vs 12.1 ± 1.5, p < 0.01) ↔ glucose ↓C-peptide in IG (2.0 ± 0.3 vs 3.0 ± 0.3, P < 0.01) ↔ IGF-I or IGFBP-1 ↑ physical component scores in IG (45 vs 40 p=0.04) ↔ mental component score ↑cravings for salt (p=0.03), and ↓cravings for starchy foods (p=0.03) and fast food fats (p=0.04) in IG ↔ cravings for high-fat foods or sweets

Anderson 2016[165] , USA	Phase 1 trial with single assignment	9 Age NR Stage 3-4b head and neck squamous cell carcinoma	4:1* KD fed by PEG followed by oral intake for 5 wks. Concurrent platinum chemo-radiotherapy	33% retention Ppts who discontinued completed a median of 6 days (range 0-8 days) on KD Trial terminated early (intended sample size 14)	6 discontinued: additional stress (n=1), grade 2/3 nausea (n=3), grade 3 fatigue (n=1), grade 4 hyperuricemia (n=1) 2 SAEs: hyperuricemia, pancreatitis	4 SAEs: parotiditis, nausea, vomiting, neutropenic fever ↑Ketones in compliant ppts (median 24 days, range 19-25 days) ↑BHB levels in compliant ppts (median 5 wks, range 4-5wks) ↔ lipid panel test at 3wks ↑ Serum oxidative stress markers with increasing days on KD
Renda 2015 and Dardis, 2017[166], USA	Phase 1/2 trial with single assignment	14 Mean age 45y (range 37-63y) Brain cancer	4:1 KD^ for 8 wks during concurrent radiation and chemotherapy, followed by a 1:1 diet during adjuvant temozolomide chemotherapy	47% recruitment 14% stopped due to tolerability Trial terminated early (intended sample size 40)	No weight loss >10% of baseline (NB - only reported in preliminary results from 6 ppts)	29% reported nausea

Rieger 2010[167] and Rieger, 2014[168], Germany	Pilot study with single assignment	20 Mean age 55y (range 30-72y) Brain cancer	KD: <60 g/day CHO consumed with 500ml highly fermented yoghurt drinks and 2 plant oils daily. Followed diet for 6-8 wks alone and for a further 6-8 wks either alone or during salvage chemotherapy (n=8)	15% discontinued after 2-3 wks (diet negatively affecting QoL)	↓ body weight (-2.2%) at 6-8 wks No SAEs attributable to diet	No grade 3 AEs 12 out of 13 evaluable ppts achieved ketosis (73% of urine samples had detectable ketosis) ↔ blood glucose and HbA1c at 6-8 wks
Zahra, 2017[169], USA	Phase 1 trial with single assignment	9 Age range 51-83y Non small cell lung cancer (n=7) Pancreatic cancer (n=2)	4:1 KD: 90% fat, 8% protein,2% CHO (KetoCal powder + food provided). KD 2 days prior to chemo-radiotherapy until end of treatment (6wks for lung and 5wks for pancreatic)	71% withdrawal in lung cancer ppts: Difficulty complying (n=4), grade 4 hyperuricemia (n=1) 50% withdrawal in pancreatic cancer ppts: Grade 3 dehydration (n=1) Average time on diet: 16.9 days (0-42) for lung and 21 days (8-34) for pancreatic ppts	↓body weight in lung (-6%) and pancreatic (-9.75%) cancer ppts	Grade 3/4 nausea (n=1), dehydration (n=1), esophagitis (n=1) Ketosis achieved in 89% Ketosis maintained in 33% ↔ blood glucose ↑ median plasma protein carbonyl content (nmol/mg) from pre- to post-diet (1.0 vs ≈1.4, p<0.05)

Artzi, 2017[170], Israel	Non randomised trial	9 (5 in IG, 4 in CG) IG: mean age 51y (range 37–69y) CG: mean age 46y (range 27–64y) Brain cancer	4:1 KD using KetoCal® formula for 2-31 months Bevacizumab, temozolomide or rindopepimut	40% adherence (self-report and urine ketones; ppt considered adherent when ketone level was >2 urine ketosis)	80% tolerance (tolerability criteria not defined)	Evidence of ketone bodies within the brain found in 67% of cases and 0% of controls

Champ, 2014[171], USA	Retrospective review	53 (6 cases, 47 controls) Mean age 54y (range 34-62y) Grade 3-4 glioblastoma	"Patient driven KD" – CHO levels below 50g/day or 30g/day if ketosis not reached Chemo-radiotherapy or adjuvant chemotherapy	NR	Grade 1 constipation (n=2) Grade 2 fatigue (n=1) No grade 3 toxicity	Confirmed ketosis in all cases ↓mean glucose in cases from 142.5 mg/dl (range 82–181 mg/dl) to 84 mg/dl (range 76–93 mg/dl) (p=0.02)
Klement, 2016[172], Germany	Case series	6 Mean age 60y (range 40-74y) Breast (n=1), prostate (n=1), rectal (n=3) and lung (n=1) cancer	KD: 80% fat and <50 g/day CHO during treatment (mean 48.2 days, range 32-73 days) Radiotherapy or chemo-radiotherapy	100% adherence rate to <50g/day CHO consumption Average energy from fat 73% Low BHB and high glucose in some ppts self-reporting as adherent	KD more satiating than previous diet (self report) General subjective feeling on diet rated as "good" 100% reported they would continue with a diet after RT ↓ weight (kg/wk) in 33% ↓FM in 50% ↔ absolute FFM ↑ FFM relative to body weight in 50%	↑ (worsening) symptom scores for fatigue, nausea/vomiting, appetite loss, diarrhoea ↑ in BHB ↔ glucose ↔ global health status and total functional scores

Attar 2015[173] and 2016[174], USA	Retrospective review	13 Age range 23-72y (mean NR) Recurrent brain cancer	Modified Atkins Diet: up to 60g/day carbohydrate (2-5% total calories) from 1-21months 9 on chemotherapy	85% adherence (range 1-21 months)	2 discontinued: weight loss (n=1), inconvenience (n=1) 1 SAE: renal calculus at 11 months	100% achieved ketosis
Randazzo, 2015[175], USA	Retrospective data registry review	596 (81 cases, 515 controls) Mean age 49.6y (range NR) Brain cancer	Self-administered "special diets" including KD, Low CHO, vegetarian/vegan Usual care	NR	NR	NR – data not stratified by diet type

*** Where feasibility variables are not included in the table they were not reported in the manuscript**
^4:1 KD: A ketogenic diet consisting of 80% energy intake from fat
↑ = increase/higher
↓ = reduction/lower
↔ = no change/no difference
≈ = approximate
Where absolute figures were provided, %s have been calculated to aid comparison
Abbreviations: AEs, Adverse Events; BHB, Beta-hydroxybutyrate; CG, Control Group; CHO, Carbohydrate; DLT, Dose Limiting Toxicities; DR, Dietary Restriction; FM, Fat Mass; FFM, Fat Free Mass; HbA1c, Glycated Haemoglobin; HPD, highest posterior density interval; IG, Intervention Group; IGF, Insulin-like Growth Factor; IGFBP, Insulin-like Growth Factor Binding Protein; NR, Not Reported; PEG, Percutaneous Endoscopic Gastrostomy; Ppts, Participants; QoL, Quality of Life; RCT, Randomised Controlled Trial; SAEs, Serious Adverse Events.

Feasibility results were varied. Of the six interventional studies, two were terminated early due to poor accrual and adherence[165, 166]. In the remaining four, the proportion of non-completers ranged from 15% to 71%. Recruitment rates were only reported in two of the studies and were less than 50% in both (42%[164] and 47%[166]) Adherence was reported in two of the interventional studies and was 40%[170] in one study and 80%[164] in the other. However, although both studies used urinary ketones different cut-offs were used to assess adherence.

Weight loss, adverse events and a description/breakdown of reasons for discontinuation of diet were the main tolerability outcomes reported. In general, weight loss was not a cause for concern on the KDs used, with loss below 10% of initial body weight in the majority of participants. Two trials also broke down weight loss into loss of fat mass and fat free mass. Both found that in spite of weight loss, fat free mass was preserved[164, 172]. Reports of grade 3/4 adverse events were rare.

Intervention effects reported included markers of metabolism such as ketones, glucose and insulin, quality of life and treatment-related adverse events. Of the seven studies that reported on ketones or βeta-hydroxybutyrate specifically (a common ketone), all reported ketosis or an increase in ketones in those on the KD. However, this was not always linked with a corresponding reduction in blood glucose[164, 167, 169, 172]. The study reported by Champ *et al* is the exception as it observed a reduction in blood glucose on KD during radiotherapy, even though participants received steroidal treatment which is known to increase blood glucose[171]. Four studies reported on quality of life[164, 167, 172, 175], one found evidence of positive effects[164], one found negative effects[167] and one found no effect[172]. We were unable to extract results from the fourth study as they were not stratified by diet type[175].

3.3.1.2 Protein restriction

Five studies of protein restriction were identified, of which four were specifically MET-restricted (Table 3-3). One study was an RCT in people with prostate cancer[176] while the remaining four were clinical trials with single arm allocation[177-180] including people with melanoma, glioma and colorectal cancer. One of the single arm trials was a phase 1 trial[179] which was followed by a phase 2 trial[180].

Table 3-3: ***Protein Restriction Results (n=5)***

Reference (author, year)	**Design**	**Population** (No. of ppts, age, site/lesion type)	**Intervention** (DR intervention, corresponding cancer treatment)	**Feasibility***	**Tolerance**	**Treatment effect**
Eitan, 2017[176], USA	RCT	38 (19 IG, 19 CG Mean age 59.26 ± 7.5y Prostate cancer	Protein restricted diet (0.8 g protein kg -1 lean body mass) Awaiting surgery (43±11 days on diet)	NR	NR	↔ EV size in either arm ↑ Levels of EV-associated LeR ↑ Y/S IRS1 ratio in neuronal-enriched EVs in IG vs CG ↓Body weight (kg) (-2.62 ± 2.18 p=<0.0001), FM (kg) (−1.37 ± 1.55 p=0.001), and BMI (−0.76 ± 0.75 p= <0.0001) in IG
Durando, 2008[177], France	Phase 1 clinical trial with single allocation	10 Median 68y (range 35-76y) 9 metastatic melanoma, 1 recurrent glioma	MET-free diet ranging from 1-4 days over 4 cycles of cystemustine chemotherapy	Ppts consumed 72.4% ± 31.5% of the MET-free diet administered	↔ BMI, plasma albumin or NRI	↓MET conc., optimal depletion obtained on day 1 (-40.7 ± 36.9% p < 0.05) Nitrogen balance (g/24h) stable and negative during MET-free diet (–2.24 ± 3.16) ↓Daily 3MH:creatinin ratio from 29.9 ± 14.9 ×10–3 at D0 to 15.9 ± 4.9 ×10–3 at D4 (p <0.05) Grade 3 thrombocytopenia (33%), neutropenia (33%) and leucopenia (20%)
Durando, 2010[178], France	Feasibility study with single arm assignment	11	MET-free diet for 3 days over 3 cycles of	Patients consumed 92.5% ± 21.8% of the MET-free diet administered	↔ BMI: 24.6± 3.vs 24.3 ± 2.9 (p=0.12)	↓MET concentrations. Day 1: -58.1 ± 19.1%. Day 3: -43.3% ± 13.9%

		Median age 70y (range 48-78y Metastatic colorectal cancer	FOLFOX chemotherapy		↔ plasma albumin: 36.0 ± 8.6 vs 36.7 ± 8.3 g/l (p=0.76)	Grade 3 neutropenia without fever (9%) No grade 3-4 non-haematological toxicities
Thivat, 2007[179], France	Phase 1 trial with single arm assignment	6 Age NR 1 recurrent glioma, 5 metastatic melanoma	MET-free diet ranging from 1-4 days over 4 cycles of cystemustine chemotherapy	NR	NR	↓Plasma MET of 48.5±4% from 23.1 ± 1.6 ug/L to 11.3 ± 0.7 ug/L (p=0.00002) Grade 3-4 thrombocytopenia (33%), neutropenia (33%) and leucopenia (33%) ↓ MGMT activity (fmol/mg of protein) 553 ± 90 to 413 ± 59 (p=0.029). Mean ↓ of 36 ± 8% No effect of duration of diet on MGMT activity after treatment
Thivat, 2009[180], France	Phase 2 trial with single arm assignment	22 Median age 62y (range 35-76y) 20 melanoma, 2 glioma	1 day MET-Free over 4 cycles cystemustine chemotherapy	Patients consumed 78±27% of the MET-free diet administered	↔ body weight (kg) (68.8±11.5 vs. 67.8±11.4, p=0.11), plasma albumin (g/l) (from 37.8±5.6 to 36.6±6.8, p=0.09) or prealbumin (g/l) (from 0.25±0.1 to 0.23± 0.1, p=0.32)	↓Plasma MET of 53.1±21.8% after 4h Grade 3-4 thrombocytopenia (36%), neutropenia (27%) and leucopenia (27%)

*** Where feasibility variables are not included in the table they were not reported in the manuscript**
↑ = increase
↓ = reduction
↔ = no change

≈ = approximate
Where absolute figures were provided, %s have been calculated to aid comparison
Abbreviations: BMI, Body Mass Index; CG, Control Group; DR, Dietary Restriction; EV, Extracellular Vesicles; FM, Fat Mass; IG, Intervention Group; Y/S IRS1; Insulin Receptor Substrate; LeR, Leptin receptor; MET, Methionine; MGMT; DNA repair protein O(6)-methylguanine-DNA methyltransferase; NR, Not Reported; NRI, Nutrition Risk Index; Ppts, Participants; RCT, Randomised Controlled Trial; 3MH, Urinary 3-methylhistidine.

MET free diets were achieved by using oral powders which participants consumed as drinks. Three of the four MET-free diet studies reported on the mean adherence to the diet which ranged from 72.4% to 92.5%[177, 178, 180]. Feasibility findings were not reported in the RCT of a protein restricted diet[176] and no recruitment or retention rates were reported for any of the studies.

Tolerability was reported in three trials of the MET restriction. There were no changes in markers of nutritional status (body weight, albumin or pre-albumin) associated with the MET-free diet[177, 178, 180]. In the protein restricted diet trial, the intervention group lost weight, but this was an aim of the trial which recruited overweight participants[176].

The main outcome of interest within the MET restriction studies was blood MET concentration. All four trials of MET-free diet resulted in a reduction in mean plasma MET concentrations (reductions ranged from 40.7 to 53.1%) which authors reported as successful reduction rates[177-180]. Outcomes of interest in the total protein restriction trial were cellular effects of the diet, specifically the effect of the diet on molecular mediators in extracellular vesicles. They found that the diet increased the levels of extracellular vesicle-associated leptin receptors and a higher Y/S Insulin receptor substrate-1 ratio in the protein restricted group, indicating improved leptin and insulin sensitivity[176].

3.3.1.3 Fasting

Four studies of fasting were identified, and all were conducted at the time of chemotherapy: one pilot RCT[160], one dose escalating study[159], one qualitative study[183] and a case series report[158] (Table 3-4). Each study utilised a different fasting protocol. Self-administered fasts ranged from 48-140 hours prior to and/or 5-56 hours following chemotherapy. Per-protocol fasts ranged from 24 hours prior to chemotherapy to 72 hours, divided as 48 hours prior to chemotherapy and 24 hours post-chemotherapy. Each study also included a different clinical population, with varying cancer types.

Table 3-4: ***Fasting Results (n=4)***

Reference (author, year)	**Design**	**Population** (no. of participants, cancer site, treatment)	**Intervention** (DR intervention, corresponding cancer treatment)	**Feasibility***	**Tolerance**	**Treatment effect**
De Groot 2013[181] and 2015[160], Netherlands	Pilot RCT	13 (7 IG, 6 CG) IG: Median age 51y (range 47-64y) CG: Median age 52y (range 44-69y) Stage 2-3 breast cancer	48 hr fast (24h before until 24h after start of chemotherapy) 3 weekly (neo) adjuvant TAC-chemotherapy	15% withdrawal	NR	↑ median blood glucose (mmol/L); IG: 5.2 to 6.8 (p=0.042), CG: 4.8 to 7.0 (p=0.043) ↓ mean IGF-1 (nmol/L) of 17% in IG (23.7 to 19.6, p=0.012), ↔ CG ↔ median insulin (mU/L) in IG, ↑ in CG group**:** 2.0 to 16.0 (p=0.043) ↔ TSH (mU/L) in IG: 1.49 to 0.42, ↓ in CG: 1.38 to 0.61 (p= 0.034) ↔ in IGF-BP3 or FT4 ↑ erythrocytes in IG (Day 7: p=0.007, 95 % CI 0.106–0.638; Day 21: p=0.002, 95 % CI 0.121–0.506) ↑ thrombocytes in IG (p=0.00007, 95 % CI 38.7–104) at day 7 ↔ leukocytes or neutrophils ↔ self-report side effects
Dorff, 2016[159] and Quinn, 2013[182],	Dose escalation	20	3 cohorts fasted before chemotherapy for 24, 48 and	Adherence: 24h fast: 67%, 48h fast: 83%, 72h fast 57%	Grade 1/2 fatigue, headache, dizziness,	↓ IGF1. **24h fast: Cycle 1:** -30% (-12 to -44%) **Cycle 2:** -31% (-45% to -13%) **48h fast: Cycle 1:** -33% (−45% to -18%) **Cycle 2**:

USA		Median age 61y (range 31–75y) Any cancer	72 h (divided as 48 pre-chemo and 24 post-chemo) Platinum based chemotherapy		hypoglycaemia, weight loss, hyponatremia and hypotension No grade 3/4 fasting-related toxicities 5% failed to regain 25% of weight lost	-20% (−37% to 1%) **72h fast: Cycle 1**: -8% (−24% to 13%) **Cycle 2**: 16% (−5% to −42%) ↔ glucose ↓ mean insulin. **24h fast**: -56%. **48h fast:** -27%. **72h fast:** -42% at 48h (data at 72 hours NR) ↓ DNA damage in 48h and 72h, but not 24h fast ↓ nausea. 24h fast: 100%, 48h fast: 87%, 72h fast: 43% (p = 0.019) ↓ vomiting. 24h fast: 83%, 48h fast: 43%, 72h fast: 0% (p = 0.003) ↔ neutropenia. 24h fast: 67%, 48h fast: 14%, 72h fast: 29% (p=0.17)
Mas, 2017[183], France	Qualitative	15 Age NR Breast cancer	Self-administered fast concurrent to chemotherapy	Main motivation to limit chemotherapy side effects Effect of fasting on tumour was not a motivation (patients felt cancer-free following surgery) Offered a chance for ppts to take an active role in treatment	13% reported AEs which stopped them fasting	Fasting was a positive experience that reduced the side effects of chemotherapy and reinforced self-esteem
Safdie, 2009[158] and	Case series	10	Self-administered fast ranging from 48-140	NR	Low grade dizziness, hunger, and	↓ in fatigue (p<0.001), weakness (p<0.00193) and GI side effects (absent) in

2010[184], USA	Median age 61y (range 44-78y) Breast (n=4), prostate (n=2), ovarian (n=1), uterine (n=1), lung (n=1), oesophageal (n=1) cancer	hrs prior to and/or 5-56 hrs following chemotherapy	headaches reported No grade 3/4 toxicities Weight loss recovered in "most" patients	46 reported cycles with fasting compared with 18 ad-libitum cycles

*** Where feasibility variables are not included in the table they were not reported in the manuscript**
↑ = increase/higher
↓ = reduction/lower
↔ = no change/no difference
Where absolute figures were provided, %s have been calculated to aid comparison.
Abbreviations: AEs, Adverse Events; CG, Control Group; CHO, Carbohydrate; DR, Dietary Restriction; FT4, thyroxine; GI, gastrointestinal; IG, Intervention Group; IGF, Insulin-like Growth Factor; IGFBP, Insulin-like Growth Factor Binding Protein; NR, Not Reported; RCT, Randomised Controlled Trial; SAEs, Serious Adverse Events; TSH, Thyroid Stimulating Hormone.

Feasibility findings were reported in both interventional studies with the pilot RCT reporting a 15% (n=2) withdrawal rate[160]. Within the dose escalation study, authors reported 67% compliance in the 24h fast, 83% in the 48h fast and 57% in the 72h fast. However, they also note that, although self-reported compliance was high in the 72h fast, it may have been subject to poorer compliance given that the IGF analysis showed lower than expected reductions in IGF1 at 72 hours[159]. No further feasibility results, such as recruitment or retention rates were reported in these studies. The qualitative study reported findings regarding the motivation behind women choosing to fast during chemotherapy for breast cancer[190]. Authors reported that the main motivation for choosing to fast was to limit the side effects of treatment, while the potential effects of fasting on the tumour was not found to be a motivating factor.

Tolerability of the fast was not discussed in the RCT. However, no grade 3/4 toxicities were reported among participants in the dose-escalating or qualitative studies [158, 159]. Grade 1/2 toxicities are listed in Table 3-4 and included dizziness, hunger, headaches and weight loss. Among the participants in the qualitative study, 13% (n=2) reported experiencing adverse events which stopped them following their self-administered fast[183]. In the case series, weight loss was reported to resolve in "most" participants following introduction of normal feeding [158]. Only 1 participant in the dose escalation study did not regain at least 25% of body weight lost during the fast between cycles and was unable to continue with the second fast, as per the trial protocol[159].

The intervention effects of interest within the fasting literature focus on biological markers of metabolism and chemotherapy toxicities. Both interventional studies found a reduction in IGF-1 associated with fasting, however the levels varied depending on the trial and length of the fast. Reductions ranged from 17.3% after 24 hours of the 48h fast[160] to 33% after the 48h fast[159]. Despite fasting, neither interventional study found a reduction in glucose, with glucose increasing after 24 hours in the RCT[160] and no changes evident in the dose escalation study[159]. Study authors suggested the use of steroidal treatment among study participants as a potential reason for the lack of glucose reduction during fasting. The two observational studies found evidence of decreased side effects from chemotherapy. This was self-reported in the qualitative study[183] (side effects that were reduced were not specified) while the case series report found a reduction in fatigue, weakness and gastrointestinal side effects in cycles completed alongside a fast when compared to cycles where cases ate *ad-libitum*[158]. These findings were similar in the dose escalating study which found a trend for

reduced nausea and vomiting in longer fasts[159] but were not seen in the pilot RCT which found no differences in self-reported AEs between groups[160].

3.3.1.4 Combined interventions

Four studies of combined interventions were identified and are summarised in Table 3-5: one RCT[185] and three case reports[186, 188, 189]. All combined some form of ketogenic or low carbohydrate diet with additional interventional aspects such as increased physical activity in the RCT[185], or additional dietary changes[186, 188, 189]. As the diets were delivered in combination with other components and the majority are based on single patient case reports, interpretation is limited. However, the RCT reported a high retention rate of 81% and found that the main side effect associated with the low carbohydrate and increased physical activity intervention was mild headaches[185]. No other feasibility outcomes were reported in these studies.

3.3.2 Ongoing/planned trials

The clinicaltrials.gov and ISRCTN databases were searched on 10th December 2018 for studies that were registered as ongoing or planned. This search identified: 13 trials of KD, one trial of a KD combined with short-term fasting, one trial of short-term fasting, five trials of fasting-mimicking diets and two trials of intermittent fasting. These are summarised in Table 3-5. This search indicates that the KD continues to be the most researched form of restriction (n=13) and the majority of these studies are in people with brain cancer (n=8). Although there are an increasing number of KD RCTs identified (n=5), three specifically identify as pilot/feasibility studies, and all have small target sample sizes (range = 12-60). An increased interest in other forms of fasting such as intermittent fasting (n=2) and fasting-mimicking diets (n=5) is also evident. Fasting RCT target sample sizes range from 30-250.

Five of the 13 ongoing/planned KD trials aim to collect primary outcomes relating to feasibility results (e.g., adherence and recruitment) (NCT 03285152, ISRCTN71665562, NCT03278249, NCT02964806, NCT03535701), while six aim to collect primary outcomes on safety and tolerability (e.g., adverse events and weight loss) (NCT02983942, NCT 02302235, NCT01754350, NCT01865162, NCT03451799, NCT02939378). For the five planned/ongoing FMD trials, only one (NCT03595540) includes a feasibility based primary outcome, while three will report on adverse events (NCT02126449, NCT03340935, NCT03595540).

Table 3-5: ***Combined Intervention Results (n=4)***

Reference (author, year)	**Design**	**Population** (No. of participants, age, site/lesion type)	**Intervention** (DR intervention, corresponding cancer treatment)	**Feasibility***	**Tolerance**	**Treatment effect**
Freedland, 2016[185], USA	RCT	40 (19 IG, 21 CG) Age NR Prostate cancer	Low CHO diet (<20 g/day) combined with moderate physical activity increased by 30 min/day for 5 days/wk Concurrent to ADT	81% retention	Mild headaches main side effect	↓ HOMA by 19% in IG compared to 7% in CG (p=0.127) at 3m ↓ weight (kg) of 9.3 in IG compared to ↑ of 1.3 in CG (p<0.001) at 6m ↓ FM of 16.2% in IG compared to ↑ of 11.0% in CG (p=0.002) at 6m ↑ bone mineral content of 0.1% in IG compared to ↓2.3% in CG (p=0.025) at 6m ↓ PSA 99% in both groups (p=0.37)
Reinwald, 2015[186] and Branca, 2015[187], Italy	Case report	1 Age 66y Breast cancer	An isocaloric KD: special amino acid formula combined with probiotic yoghurt containing vitD binding protein macrophage activating factors and injections of vitD, oleic acid and vitD binding protein 3 weeks prior to surgery	NR	NR	Change in gene expression to HER2 -ve Increase in progesterone expression (20 vs <1%) No invasion of blood or lymph vessels around the tumour ER and Ki-67 markers were unchanged

Iyikesici, 2017[188], Turkey	Case report	1 Age 29y Triple negative breast cancer	Chemotherapy administered after a 12h fast followed by 5-10 units of insulin. Patient also consumed a KD for duration of treatment	Patient adhered to KD (urinary ketones present at each visit)	NR	Pathological complete response
Zuccoli, 2010[189], Italy	Case report	1 Age 65y Brain cancer	Self-administered post-operative fast followed by a calorie restricted KD with chemo-radiotherapy. KD: 600ckal/day using Keto-Cal® 4:1 supplemented with multivitamins. After approx. 2 months on restricted KD, patient switched to a calorie restricted non-KD (600kcal/day) for 5 months.	NR	Karnofsky performance status: 100% during diet Hyperuricemia on restricted KD so patient was switched to a non-KD calorie restricted diet. Hypoproteinemia on restricted diet, resolved by increasing dietary protein to 7g/day for one month. ↓ bodyweight (-9%) after fast and -22% after restricted diet	↓ blood glucose: -50% after fast and -53.3% after restricted diet ↑ ketones: from 0 (baseline) to 2.5mmol/L after fast and after restricted diet

*** Where feasibility variables are not included in the table they were not reported in the manuscript**
↑ = increase
↓ = reduction
Where absolute figures were provided, %s have been calculated to aid comparison.
Abbreviations: ADT, Androgen Deprivation Therapy; CG, Control Group; CHO, Carbohydrate; DR, Dietary Restriction; ER, Estrogen receptor; FM, Fat Mass; HER-2, Human Epidermal Growth Factor Receptor 2; HOMA, Homeostatic model assessment; IG, Intervention Group; KD, Ketogenic Diet; m, months; NR, Not Reported; PSA, Prostate-Specific Antigen; RCT, Randomised Controlled Trial, VitD, Vitamin D.

Table 3-6: ***Planned/Ongoing Trials***

Trial Registration	Trial design	Participants (target recruitment number and type of cancer)	Primary outcomes	Planned start and end dates
Ketogenic Diets				
NCT03285152	Feasibility RCT	30 Endometrial	No. of patients that complete the study	Aug 2017- Aug 2019
NCT02983942	Pilot RCT	50 Primary Central Nervous System Lymphoma	No. and incidence of treatment related AEs	Jan 2017 – Dec 2019
ISRCTN71665562	Pilot RCT	12 Glioblastoma	Retention rate	Jul 2016 – June 2019
NCT02302235	RCT	42 Glioblastoma	1. Survival time 2. Time to progression (MRI assessed) 3. Incidence of AEs	Feb 2014 – Dec 2018
NCT01754350	RCT	50 Glioblastoma	Progression-free-survival rates 6 months after reirradiation	May 2013 – June 2018

NCT03278249	Feasibility trial (single arm)	30 Glioblastoma	Ketosis (measured by serum BHB)	Sep 2017 – Jan 2021
NCT01865162	Pilot trial (single arm)	6 Glioblastoma	Safety evaluation	Jan 2013 – Jan 2019
NCT01535911	Pilot trial (single arm)	16 Glioblastoma	Brain tumour size response (MRI assessed)	Apr 2012 – June 2019
NCT03451799	Clinical trial (single arm)	Glioblastoma	Safety assessed by weight loss and AEs	Apr 2018 – Sep 2020
NCT02964806	Crossover trial	30 Pancreaticobiliary Cancer	Diet intake rate	Nov 2016 – Oct 2017
NCT02939378	Non-randomised trial (2 arms)	60 Glioblastoma	No. of participants with AEs	Oct 2016 – Dec 2018
NCT03535701	Non-randomised trial (2 arms)	15 Breast	1. Adherence 2. Change in psychosocial measures 3. Change in physiologic outcomes	Oct 2017 – Aug 2019
NCT03194516	Observational	12 Prostate	Weight loss at 8 weeks	June 2017 – May 2021

Short-term Fast				
ISRCTN17994717	Feasibility RCT	30 Colorectal	Adherence, recruitment, retention and data completion rates Acceptability and tolerability	Oct 2017 – Apr 2021
Fasting Mimicking Diets				
NCT02126449	RCT	250 Breast	1. Rate of grade 3/4 toxicity 2. Rate of pCR	Feb 2014 – Dec 2019
NCT03700437	RCT	40 Lung	Effect of diet on circulating tumour cells	Oct 2018 – Dec 2020
NCT03340935	Feasibility trial (single arm)	85 Any cancer	AEs	Feb 2017 – June 2018
NCT03595540	Pilot trial (single arm)	60 Breast and colorectal	1. % diet consumed 2. Diet related AEs	Nov 2017 – Sep 2020
NCT03454282	Clinical trial (single arm)	100 Breast and melanoma	Change in peripheral blood mononuclear cell	May 2018 – Dec 2020
Intermittent Fasts				
NCT03162289	RCT	150 Breast	Change in FACT-G QoL score	May 2017 – May 2022
NCT02710721	RCT	60 Prostate	Change in FACT-P QoL score	April 2016 – Dec 2019
Ketogenic Diet combined with Short-Term Fast				

NCT02286167	Clinical trial (single arm)	25 Glioblastoma Multiforme	Dietary adherence rates	Nov 2014 – April 2019

Abbreviations: AE, Adverse Events; BHB, Beta-hydroxybutyrate; MRI, Magnetic Resonance Imaging; pCR, Pathological Complete Response; QoL, Quality of Life; RCT, Randomised Controlled Trial

3.4 DISCUSSION

3.4.1 Main findings

Few studies have been published on DR during treatment for cancer to date, particularly when the data are stratified by restriction type. More studies are currently in progress and due to complete recruitment within the next three years, suggesting DR is a research area of growing interest. However, most ongoing trials are early-stage studies with small sample sizes. These may allow us to further understand the feasibility of conducting such studies but will not enable conclusions to be drawn about the efficacy of these interventions. Large studies with long-term outcomes are needed to definitively address these questions.

Our findings show that the most commonly studied form of DR is the KD. As with the previous review of KD in adults with cancer not specifically receiving treatment for cancer, we found the 4:1 diet to be the most common form being used in conjunction with treatment[104]. The previous review concluded that adherence rates were low, and our review confirms the potential issues surrounding adherence when using KD alongside treatment for cancer. Adherence results were varied, with different definitions of adherence and tolerability used, making comparisons of adherence to the different forms of the KD difficult. This, in combination with the early termination of two of the KD trials, suggest that further research into improving acceptability of KDs may be warranted. For example, there could be the potential for improved adherence and retention in KD studies with lower ratios of fat:carbohydrate than the 4:1 diet whilst still achieving favourable metabolic changes [169]. Furthermore, as most studies of KD reported some issues with tolerability and weight loss, it is possible that there could be concerns with palatability or sustainable behavioural change.

The results of protein restriction research suggested that MET-free diets were adhered to well with limited tolerability issues. However, the diets were provided over a short amount of time as oral solutions. It is less clear how well general protein restriction as part of a low protein meal-based diet is adhered to, as only a single trial of overall protein restriction has been conducted, which did not report feasibility outcomes.

Very few studies of fasting have been conducted. Overall, the studies to date have found that participants are able to follow short-term fasts, although length of interventions varied, and it is unclear whether longer fasts have lower adherence. As with the other DR methods, adverse events related to

fasting did not appear to affect adherence in the majority of studies, with the exception of the qualitative study[183]. This may be because participants in that study were self-administering the fast and not receiving clinical support. The qualitative study did highlight, however, that fasting was a positive experience for the majority of participants and that women felt it helped to reduce the side effects of chemotherapy. It also identified that fasting was used as a strategy to cope by allowing participants to feel more involved in their treatment[190]. As with the research on KDs, fasting appears to result in a reduction in IGFs. However, it remains unclear whether it also results in a decrease in blood glucose. This may be due to steroid treatment received alongside chemotherapy, which is known to increase blood glucose levels. One interventional and two observational studies found some evidence of reduced toxicities in fasted participants, however the evidence is limited by the small number of trials and small sample sizes included.

Findings from each DR type identified poor reporting of feasibility results, that could help to inform future research. For example, of the 23 studies, only two reported overall recruitment rates and nine reported on adherence. Measures of adherence also varied between trials, even for trials of the same intervention type. This highlights a need for improved reporting in early-stage trials, to try and improve data on feasibility outcomes, so that future trial can more easily identify whether an intervention will be feasible to test in larger scale trials. For example, future trials could ensure they follow the reporting guidelines set out by the CONSORT extension for randomised pilot and feasibility trials, to ensure accurate and consistent reporting of feasibility findings.

Overall findings suggest that dietary restriction interventions were safe. As discussed in section 1.2, DLTs are defined as grade 3, or higher, toxicities (graded according to CTCAE criteria). The majority of adverse events reported in the included studies were grades 1-2, with no grade 3-4 toxicities reported in short-term fasting, and only a limited number of serious adverse events or grade 3 toxicities reported in KDs. Although these findings are limited by the small sample sizes of included studies, the preliminary findings from early-stage research, at least, suggest that DR interventions are safe to introduce in people receiving treatment for cancer. However, it is also important to note that eligibility criteria for trials may limit the inclusion to people who are less likely to suffer adverse events related to restricting their diet e.g., people with normal BMI (BMI 18.5-24.9) or fewer comorbidities. As such, even though studies suggest safety of these interventions, eligibility criteria should still be carefully considered in future trials to ensure participant safety.

3.4.2 Future research

Larger, adequately powered RCTs will be required in order to study the efficacy of each DR intervention type to reduce treatment side effects or improve outcomes. Within KD research, further exploration of issues associated with adherence is warranted if larger trials are to test this intervention. There is a current lack of in-depth qualitative work conducted in this area, which may help in exploring the reasons for non-compliance in trials, especially if tolerability is high.

While research into MET-free diets suggest that trials of this intervention are feasible, definitive RCTs with larger sample sizes are required to ascertain whether these diets result in reduced treatment side effects or improved outcomes. Further research into adherence to and tolerability of general protein restricted diets is required in order to understand the feasibility of conducting this form of intervention alongside treatment of cancer. It is also not clear whether this diet could be introduced to people with normal weight without resulting in significant weight loss, as the only trial to date was in people who were overweight.

Conflicting findings regarding blood glucose levels suggest further research into the effect of DR on this marker is required. Attention should also be paid to the use of steroid treatment alongside chemotherapy, to investigate whether increased blood glucose seen with these drugs limits the potentially protective effect of DR. In a current study of fasting-mimicking diets the investigators have chosen to omit dexamethasone treatment[191]. However, on a pragmatic level, it would also be of interest to explore whether IGF reduction alone is able to induce metabolic changes that would be sufficient to achieve a reduction in toxicity, even in the presence of dexamethasone. Particularly as two observational and one interventional study found some evidence for reduced side effects when chemotherapy was provided as standard. Reporting on the type of weight-loss resulting from the fast would also be of interest, to ascertain whether fat is lost while lean muscle mass is retained, as has been the case in KDs.

The issue of poor reporting on feasibility results identified in this review may continue to be an issue, as confirmed by the low proportion of planned/ongoing trials which included feasibility and tolerability measures as primary outcomes. Future studies should aim to include improved reporting on these measures, to inform and improve future research in this area.

3.4.3 Strengths and limitations

While some aspects of DR have been reviewed previously[62, 104], this scoping review employed a systematic search of the literature on the different forms of DR during treatment for cancer, to collate the research to date. It followed a rigorous protocol that was developed prior to the literature search and made publicly available to aid transparency of the review procedures[162]. Although every effort was made in the search to identify all relevant texts, it is possible that some studies of DR during treatment for cancer have been missed.

This review was the first review to implement a systematic search strategy to identify the research in DR during cancer treatment. The search was not limited by language or date of publication. It allowed the research to date, to be mapped out so that it can be referred to when designing further trials in this area. By providing information on feasibility outcomes, it has highlighted the need for improved reporting in this area and identified potential issues regarding recruitment and adherence in the studies that did report on this. Reporting the tolerability outcomes of interventions provides some information to researchers on the safety of interventions. And finally, by providing information on treatment effect outcomes that have been reported to date, it collates information that could be useful in the design of definitive trials, such as identifying outcomes of interest and providing effect sizes for sample size calculation. However, these results must be interpreted with caution, at least on an individual basis, because, as identified in this review, much of the data comes from early-stage research in small sample populations.

In order to acknowledge the emerging nature of DR research, a scoping review process was followed, which included data from observational and single-arm studies. This allowed us to consider the breadth of previous research in an emerging field, helping to inform future studies. However, this also means that the quality of studies has not been assessed against the standards commonly used in systematic reviews of RCTs. So, while the treatment outcome results reported in this review can be used to inform future trials, they must not be interpreted as efficacy results.

This approach has allowed us to summarise the emerging research on DR in cancer treatment, highlight some issues that should be considered when designing further studies in this area and identify gaps in the literature.

3.4.4 Conclusion

DR regimes are a potential tool to help reduce the toxicities associated with cancer treatment. However, the limited number of studies to date have had small samples and have not been designed to specifically test the efficacy of these interventions. DR is, however, a growing research area with further trials being conducted. Definitive RCTs are required to assess the efficacy of DR during cancer treatment on reducing treatment related toxicities or improving treatment outcomes. This scoping review has highlighted the potential problem of adherence issues and as such suggests further research into improving dietary compliance is conducted before larger efficacy trials are conducted. Further research into the effect of DR interventions on cellular metabolism when used in combination with treatment is also warranted.

3.5 UPDATED SEARCH SUMMARY

On 18th February 2021, an updated search was conducted on the trials listed as ongoing in Table 3-6 at the time of the scoping review publication. An updated search for newly registered trials was also completed.

This search identified that a further five trials of dietary restriction had been completed, with results published. These trials included a total sample size of 199 (range 8-129). Four of the trials were of KDs in people with glioblastoma[192-194]. Two of these trials followed the same treatment protocol, but with different patient groups; recurrent glioblastoma in one trial and newly diagnosed glioblastoma in the second. However, as both trials were terminated early, due to low recruitment, the authors reported the combined results of both protocols[193]. The fifth trial was of a FMD in people with breast cancer[195]. The additional study results are summarized in Table 3-7, below.

Table 3-7: ***Summary of completed trials found in updated search completed on 18th February 2021 (n=4)***

Reference (author, year, country)	**Design**	**Population** (No. of ppts, age, site/lesion type)	**Intervention** (DR intervention, corresponding cancer treatment)	**Feasibility**	**Tolerance**	**Treatment effect**
Martin-McGill, 2020[192], UK	Randomised pilot study	12 Median age 57y (range 44-66y) WHO grade 4 glioblastoma	Modified KD or medium chain triglyceride KD for three months Standard of care: radiotherapy and temozolomide chemotherapy	Recruitment rate: 28.6% Retention: 33.3% (4/12) Median duration to discontinuation: 38days (range: 36-40days)	Five grade 1 AEs: hypokalemia (n = 2), hypernatremia (n = 1), hypocalcaemia (n = 1) and a partial seizure (n = 1) Three SAEs, unrelated to dietary intervention	Ketosis achieved in 79.7% of MCTKD (n = 3) and 79.3% of MKD (n= 3) (defined as urinary ketone level of ≥4 mmol/L within first 6 weeks)
Klein, 2020[193], USA	Non-randomised, prospective pilot study	8 Mean age 49.8y (range 40–64y) Newly diagnosed (n=4) or recurrent (n=4) glioblastoma	4:1 [fat]:[protein + CHO] ratio KD calorie restricted to 1600kcal/day for 6 months, provided as a total meal replacement Treated adjunctively to	Slow recruitment led to early termination and combined reporting of two related trials Ratio of eligible screened: enrolled patients was 3.37	Mild-moderate AEs of hunger, dizziness, fatigue and constipation Hunger and weight loss lead to lifting of calorific restriction after 1	↑ in daily urine ketone levels ↑ in cholesterol and triglyceride levels by > 20% in 3 patients and ↓by > 20% in 1 patient from baseline to end of trial

Reference (author, year, country)	**Design**	**Population** (No. of ppts, age, site/lesion type)	**Intervention** (DR intervention, corresponding cancer treatment)	**Feasibility**	**Tolerance**	**Treatment effect**
			radiation and temozolomide	62.5% retention Reasons for discontinuation: disease progression (n=2) and diet restrictiveness (n=1)	month in all participants No treatment related SAEs	
Voss, 2020[194], Germany	RCT	50 IG: median age 56y (range 39–71y) CG: median age 58y (range 26-75y) Recurrent glioblastoma or progressive glioma	IG (n=25): One cycle of KD-IF for 9 days (comprised KD on days 1-3 and 7-9, and a fast on days 4-6) CG(n=25): calorically unrestricted diet Combined with reirradiation	Recruitment rate NR IG retention: 80% CG retention: 88%	9 AEs reported (IG: n=4; CG: n=5) AEs were headache, nausea and epileptic seizures No treatment related SAEs	Ketosis achieved in 17/20 in IG at day 6 ↓glucose by –11.2 ± 16 mg/dL at day 6 in IG ↔ glucose in CG ↓ weight of –2.1 ± 1.8 kg ↔ insulin, IGF-1, cholesterol,

Reference (author, year, country)	**Design**	**Population** (No. of ppts, age, site/lesion type)	**Intervention** (DR intervention, corresponding cancer treatment)	**Feasibility**	**Tolerance**	**Treatment effect**
						↔ Progression free survival or overall survival
De Groot, 2020[195], Netherlands	RCT	129 IG: median age 49y (range 31-71y) CG: median age 51y (range 27-71y) HER2-negative stage II/III breast cancer	IG (n=65): FMD for 6 days (3 days prior to and 3 days during neoadjuvant chemotherapy) CG (n=64): regular diet for 6 days (3 days prior to and 3 days during neoadjuvant chemotherapy) 6 cycles of neoadjuvant FEC-T (n=30) or 8 cycles AC-T chemotherapy (n=99)	IG compliance: 20% all cycles, 50% 2 cycles. CG compliance: 92.2% all cycles	↔in toxicity between intervention groups	↔ in overall pCR rate between the two groups (10.8% in FMD group versus 12.7% in control group; OR 0.830, 95% CI 0.282–2.442, P = 0.735) A radiologically complete or partial response occurred more often in IG (OR 3.168, P = 0.039) ↔ in Quality of Life scores between groups ↓ blood glucose, insulin and CRP in IG compared to CG ↔ in IGF-1 or IGF-BP3 between groups

↑ = increase/higher
↓ = reduction/lower
↔ = no change/no difference
Where absolute figures were provided, %s have been calculated to aid comparison.
Abbreviations: AC-T, Doxorubicin, cyclophosphamide, paclitaxel chemotherapy; AEs, Adverse Events; CG, Control Group; CHO, Carbohydrate; CI, Confidence interval; DR, Dietary Restriction; FEC-T, 5 fluorouracil, epirubicin, cyclophosphamide, docetaxel chemotherapy; FMD, Fasting Mimicking Diet;

Reference (author, year, country)	**Design**	**Population** (No. of ppts, age, site/lesion type)	**Intervention** (DR intervention, corresponding cancer treatment)	**Feasibility**	**Tolerance**	**Treatment effect**

IF, Intermittent Fast; IG, Intervention Group; IGF, Insulin-like Growth Factor; IGFBP, Insulin-like Growth Factor Binding Protein; KD, Ketogenic diet; NR, Not reported; OR, Odds Ratio; pCR, pathologic complete response, RCT, Randomised Controlled Trial; SAEs, Serious Adverse Events;

Of the four KD trials, different forms of a KD were used in each trial and were used in combination with energy restriction in two trials[193, 194]. Overall, the findings from the KD studies in this updated search confirmed that recruitment, retention and adherence continue to be a common problem within some KD trials; one of the trials referenced low recruitment and retention[192] and two trials were terminated early and results combined for publication[193]. The third trial of KD did, however, achieve the required recruitment target (50 participants) and reported high retention rates, though the overall recruitment rate was not reported[194]. Combined, these trials also confirmed that the various forms of KD were successful at achieving ketosis and were well tolerated, in terms of adverse events, with no SAEs reported. However, in the trial of a calorie restricted KD, the calorie restriction aspect of the diet was removed for all participants due to weight loss in the first month.

The updated search identified that the first trial of a FMD has been completed with results published. "The Dietary Restriction as an Adjunct to Neoadjuvant Chemotherapy for HER2 Negative Breast Cancer (DIRECT)" trial randomised 131 women with HER2-negative stage II/III breast to either a FMD or their regular diet for 3 days prior to and during neoadjuvant chemotherapy[195]. One participant from the FMD group withdrew consent prior to treatment and one participant from the control group was deemed ineligible following randomisation due to liver metastases. Of the remaining 129 participants, 65 received FMD and 64 received their regular diet. In the FMD arm, 43 participants (66%) were not compliant for half of the 4 cycles, and the main reason for non-adherence was dislike of "distinct components" of the diet. The authors did not, however, provide further information on which specific components were disliked by trial participants. In the control arm, five participants (8%) were not compliant with their regular diet and opted to fast during one or more of their cycles. No differences in adverse events were found between the two groups. The authors noted that this finding was of interest because participants in the FMD group did not receive standard dexamethasone treatment, which is usually given prophylactically to reduce treatment toxicities, while those in the control group continued to receive dexamethasone. This suggests that the FMD may negate the need for prophylactic dexamethasone, due to its affect in treatment toxicities. A radiologically complete or partial response to treatment, measured by MRI prior to surgery, following chemotherapy treatment, and assessed according to RECIST criteria[196], was found to occur more often in patients using the FMD compared to regular diet (OR 3.168, 95% CI 1.062–9.446, P = 0.039)[195]. Findings from this first study of FMD during chemotherapy suggest that the diet is feasible and safe, though efforts to improve adherence across more cycles of chemotherapy is warranted. Further trials will be required to fully test the efficacy of the

intervention in regard to its ability to reduce chemotherapy toxicities and improve outcomes. Further research into how to improve adherence is also warranted.

An updated search of new or ongoing trials listed in the clinicaltrials.gov and ISRCTN databases was also completed on 2nd March 2021. This search identified: four trials of KD, one trial of short-term fasting, two trials of fasting-mimicking diets and two trials of time restricted eating. These are summarised in Table 3-8. The new trials confirm that dietary restriction during cancer treatment continues to be an intervention of interest and that the KD remains the most researched form of restriction. One new form of intermittent dietary restriction identified in this search is the concept of time restricted fasting. This form of dietary restriction involves restricting food intake to a 6-10 hour period during the day[197]. It has been found to induce metabolic benefits in animal models, by reducing insulin levels, and subsequently inhibiting breast cancer tumour growth[198]. In human studies, it has been found to reduce body weight and improve glucose tolerance[199]. In addition to this, epidemiological studies have also found that a prolonged overnight fast is associated with a reduced risk for breast and prostate cancer[200]. Since this intervention produces similar biological effects to other forms of dietary restriction (i.e., insulin reduction), and the potential for reduced tumour growth, it is an intervention of interest for use alongside chemotherapy. The two trials of time restricted eating identified in this search are exploring the effect of prolonged overnight fasting on tumour biology and treatment toxicity (NCT04722341 and NCT04708860), including the ability of the intervention to counteract the negative metabolic effects of cancer treatment (NCT04708860).

Table 3-8: ***Updated search of newly registered trials***

Trial Registration	Trial design	Participants (target recruitment number and type of cancer)	Primary outcomes	Planned start and end dates
Ketogenic Diets				
NCT03962647	Single arm feasibility	30 Oestrogen Receptor-positive Breast cancer	Completion rates	July 2019 – Feb 2023
NCT04750941	Non-randomised, single assignment trial	42 Follicular Lymphoma or Endometrial Cancer	Objective response rate	March 2021 – Dec 2021
NCT04316520	Single assignment pilot	20 Metastatic Renal Cell Carcinoma	Tolerability	July 2020 – May 2024
NCT04631445	RCT	40 Metastatic Pancreatic Ductal Adenocarcinoma	Progression free survival	Nov 2020 – March 2023
Short-term fasting				
NCT04387084	Single arm feasibility	16 Advanced/metastatic skin cancer	Safety, tolerance and adherence rates	June 2020 – June 2023
Fasting Mimicking Diets				
NCT04292041	Observational cohort	40 Prostate cancer	Change in weight, metabolic biomarkers and quality of life	Jan 2019 – June 2020
NCT04248998	Randomised parallel assignment trial	90 Triple-negative breast cancer	pCR rate	May 2020 – Dec 2024

Time-restricted eating or prolonged nightly fasting				
NCT04708860	Feasibility single arm	30 Metastatic breast cancer	Enrollment and adherence rates	Jan 2021 – July 2022
NCT04722341	RCT	300 Colorectal cancer	Treatment related toxicities	April 2021 – Dec 2026

Abbreviations: pCR, Pathologic Complete Response; RCT, Randomised Controlled Trial

3.6 IMPLICATIONS FOR THESIS

As outlined in Chapter 2, one of the purposes of this scoping review was to inform the design and development of a feasibility RCT of fasting during chemotherapy. The findings of this review were used in several ways when developing the trial protocol. For example, the review highlighted a paucity of qualitative research on aspects such as acceptability of DR interventions. Only one piece of qualitative research had been conducted on fasting at the time of chemotherapy[190] and this was in people following a self-administered fast (i.e. fasts of variable lengths which they chose to initiate themselves, outside of a trial setting), as opposed to a per-protocol fast. The RCT that was developed as part of this PhD (see chapter 4) includes a qualitative investigation of participant experiences of following a short-term fast during chemotherapy. It will, to our knowledge, be the first piece of in-depth qualitative work to be conducted in trial participants who have been asked to fast at the time of chemotherapy.

The review also highlights how reporting of feasibility outcomes is poor, even in early-stage informative research studies. This means that the SWiFT feasibility RCT described in Chapter 4, will add to the literature, by providing high quality data on recruitment, retention and adherence rates to a short-term fasting intervention during cancer treatment.

Previous research has shown that dietary interventions which include behaviour change theory are more successful at inciting behaviour change[123]. Without a deeper understanding of the experiences of people following a short-term fast while being treated with chemotherapy, it is difficult to identify any health behaviour theory that would be useful when delivering the intervention. For example, what are the perceived barriers or facilitators to following the fast as per protocol? As can be seen in Tables 3-2 to 3-5, none of the trials included in this review reported that they measured behavioural change concepts. Similarly, the methods described in the short-term fasting intervention studies did not focus on behavioural change techniques or identify themselves as behaviour change interventions, and no interventions were reported to be designed using behavioural change theory. Seven of the KD intervention studies did provide information on how the dietary intervention was delivered, with some behaviour change techniques being implemented. These included provision of dietary education from a dietitian[166, 192, 201], regular counselling from a dietitian during the trial[172, 201], tailored meal-plans[192], sample meal plans and recipes[165, 168, 172, 201] or provision of books on KDs[171, 172]. One intervention was delivered in a hospital setting, where all food was prepared for participants, negating the need for participants to prepare the food themselves[169]. However, although some of the

KD studies described how behaviour change techniques were implemented during intervention delivery, none of the studies described using behaviour change theory to inform the intervention design. And no behaviour change concepts were measured as part of intervention evaluation. Therefore, the qualitative work outlined in chapter 4 of this thesis may identify potential behaviour change theory which could be utilised when designing future protocols of short-term fasting at the time of chemotherapy. In this way the qualitative work can be used as a tool to increase adherence in future trials, with the aim of improving feasibility of conducting these types of interventions.

The conceptual framework for selecting studies was based on the concept of DSR. DSR states that the protective state adopted by non-tumour cells is partially mediated by a reduction in cellular glucose and IGFs. However, this review has highlighted that, within fasting trials, although IGFs were reduced following short-term fasts, glucose did not appear to be reduced. Although adequately powered trials would be required to definitively test whether fasting affects glucose levels for those receiving chemotherapy, a feasibility trial assessing this outcome could give more information on the parameters of this measure on which to base sample size requirements. As discussed within the findings in section 3.4.2, the fact that glucose reduction was not observed, may be due to the use of the steroid treatment (dexamethasone) that is routinely given alongside chemotherapy. There is justification, therefore, for either continuing to administer steroid treatment or omitting it in future research. On the one hand, if the steroid treatment is potentially attenuating the effects of the fast, there is a rationale to omit it to provide the best chance possible for the intervention to achieve the metabolic changes required to have an effect. However, the fact that some feasibility studies report a reduction in side effects, even when chemotherapy was delivered alongside standard dexamethasone treatment, means there is also an argument for further studying the effect of the fast in a "real life setting." This second approach fits more with the pragmatic approach taken within this thesis and will be discussed further in the methods section of the RCT chapter (Chapter 4).

During the updated search for this scoping review, described in section 3.5, an additional form of fasting that was not originally described in the background of the review, or included in the scoping review prior to the update, was identified. This was the time restricted fasting intervention. Therefore, it is clear that this is a relatively new diet of interest in the oncology field. As no results have been published from these trials yet, it remains to be seen whether this form of restriction will resolve some of the potential issues of adhering to short-term fasts that last longer than 8-12 hours. Data will also be required to see if

these forms of fast achieve the metabolic changes that may induce DSR when utilised alongside chemotherapy, such as reduced glucose and IGF levels.

One recommendation for future research in short-term fasting during cancer treatment is to monitor body composition and type of weight loss (i.e., fat mass and/or fat free mass) as a side effect of short-term fasting, instead of using bodyweight alone, as has been explored in research into KDs[202]. This will provide a fuller understanding of the potentially negative side effect of energy restriction, as muscle loss is more clinically important than weight loss due to fat or water loss, due to the associations with sarcopenia and cachexia. We therefore aim to further understand the effect of short-term fasts in people undergoing chemotherapy by measuring sarcopenia before and after their trial participation. Again, including this in the feasibility stage, will allow us to gather information on the practicalities of measuring this as an outcome in a definitive trial, as well as providing measurement parameters in the stage 2/3 colorectal cancer population.

Finally, synthesising both the previous research and the ongoing/planned research registered on clinicaltrials.gov and ISRCTN databases, confirmed that one clinical group that had not been included in other studies of fasting were those undergoing chemotherapy for colorectal cancer. The RCT reported in chapter 4 will be the first to study short-term fasting in this population and as such will be able to identify any feasibility issues which may be particular to this group.

Key Messages

1. Dietary restriction during cancer treatment is a topic of emerging research interest as studies suggest it may reduce treatment toxicities.
2. KDs are the most studied form of dietary restriction, to date.
3. To date, trials have comprised small sample sizes, and the efficacy of dietary restriction interventions for reducing treatment toxicities is not yet known.
4. Overall, diets appear to be safe and tolerated well, as most adverse events reported in early-stage trials, including weight loss, have been grade 1-2. Few grade 3 toxicities, or serious adverse events have been reported.
5. Feasibility outcomes, such as recruitment, retention and adherence rates, are often not clearly reported, and future trials should aim to improve reporting, in order for feasibility to be fully assessed.

6. Adherence to DR interventions is variable and further research into improving adherence is warranted.
7. Colorectal cancer was identified as one cancer type that has not yet been included in studies of short-term fasting.
8. Very little qualitative work has been conducted to date on this topic, and further qualitative work could be useful for identifying ways to improve adherence in future trials.

Chapter 4 PROTOCOL AND INITIAL RECRUITMENT TO THE FEASIBILITY RCT: "SHORT-TERM WATER-ONLY FASTING PRIOR TO CHEMOTHERAPY TRIAL" (SWIFT)

The "Short-term, Water-only Fasting Prior to Chemotherapy Trial" (SWIFT) is a feasibility randomised controlled trial (RCT) of short-term fasting in people receiving chemotherapy for colorectal cancer and comprised the second project within this thesis of dietary restriction during cancer treatment. However, participant recruitment to this trial was delayed by the COVID-19 pandemic, which resulted in suspension of the trial almost immediately after it had opened to recruitment. For this reason, the SWiFT trial is ongoing at the time of writing. This chapter therefore details the methods (Section 4.3) of the RCT protocol, which have been published in Pilot and Feasibility Studies[2], and, in an addendum to the published methods, this chapter provides an update on the recruitment to the trial so far. It also provides further discussion on some of the design choices made, during protocol development and on the implications of this for future research.

Development of the trial protocol was led by ES with input into the concept and design from CA, CP, GH, AN and clinical colleagues at University Hospitals Bristol and Weston NHS Foundation Trust and North Bristol NHS Trust. ES also managed the set-up of the trial. This included site identification, feasibility and selection, obtaining Sponsor and Research Ethics Committee approval, site costings and contract review, conducting Site Initiation Visits, training site research staff in the protocol and, finally, obtaining confirmation of capacity and capability from site R&D departments. The trial database and case report forms were designed by ES with input from a database manager.

4.1 BACKGROUND

As discussed in chapter 1, data from cell line studies and animal models suggest that differential stress resistance (DSR) can be exploited during chemotherapy to limit the toxic effects of chemotherapy in healthy cells while leaving tumour cells susceptible to treatment. However, it is unclear how well these findings translate to humans. As identified in chapter 1, and through the scoping review described in chapter 3, people undergoing chemotherapy for colorectal cancer are one population who have not been included in preliminary research into short-term fasting at the time of chemotherapy. Further

research into the feasibility of a trial evaluating short-term fasting prior to chemotherapy for colorectal cancer is therefore warranted.

By inducing a differential stress resistance between healthy and tumour cells, fasting prior to standard CAPOX administration may offer increased protection of non-cancer cells during chemotherapy. This study aims to test the feasibility of a pre-chemotherapy, 36-hour, water only fast in people receiving CAPOX chemotherapy for stage 2/3 colorectal cancer. The trial will take a pragmatic approach that will fit into current standard treatment for this patient group.

This will allow for assessment of the recruitment and adherence to a fasting intervention in this population. It will also explore some of the potential effects of the fast on blood glucose, growth factors, and side effects, the primary outcomes that would be measured in a definitive trial.

4.2 PROTOCOL DEVELOPMENT

This section provides further information on some of the design choices made in the development of the SWiFT protocol.

4.2.1 A pragmatic approach

The SWiFT trial protocol uses a pragmatic trial design, in keeping with the overall methodology of this thesis. Unlike efficacy/explanatory trials, which aim to determine the effectiveness of a treatment in ideal conditions, pragmatic or effectiveness trials aim to study the treatment of interest under more real world clinical settings[203]. Testing the feasibility of the fasting intervention under usual care settings, increases the ability of results of the trial to inform the applicability of rolling out the study in a definitive pragmatic trial, which in turn will inform how the intervention could be delivered in actuality (i.e., clinical practice), outside of a trial setting[204].

For this reason, it was important to consider how the fasting intervention would be delivered outside of the trial. Mapping the trial participant pathway as closely as possible to the routine clinical pathway was important for two reasons. Firstly, it would reduce both participant and research staff burden, by excluding the need for any additional research visits. Secondly, it would allow us to test the feasibility of conducting the intervention within the “real world” clinical setting which would be followed if the intervention were rolled out in the future.

This approach drove a number of decision-making processes in the design of the protocol and will be discussed in further detail below.

4.2.1.1 Timing of fast

Participants will be asked to fast prior to the start of each of their first three chemotherapy cycles. As such, the fast will be a) prior to the administration of oxaliplatin which is the most toxic of the two chemotherapy drugs that comprise CAPOX chemotherapy and is administered first[205, 206], and b) negates the issue of capecitabine needing to be taken with food, as per recommended procedure[207]. Asking participants to fast for three consecutive cycles also allows us to explore whether adherence is maintained over a number of cycles, when toxicities may accumulate.

4.2.1.2 Duration of fast

As discussed in chapter 1 (section 1.3.2), one of the mediating mechanisms behind DSR is thought to be the reduction in Insulin Like Growth Factors (IGFs) caused by energy restriction. As such, the potential effect of short-term fasting on IGF levels was taken into account when considering what length of fast to implement in this trial. A decrease in IGF-I levels in response to a short-term fast in humans is seen within 36–120 hours of fasting[44]. As previous research has suggested that fasts of 48 and 72 hours may be subject to poorer adherence[159], participants will be asked to fast for 36 hours prior to the start of chemotherapy administration.

4.2.1.3 Potential interactions with concomitant medication

Dexamethasone is an antiemetic routinely given to patients receiving moderately emetogenic chemotherapy regimens such as oxaliplatin[36, 208] and is prescribed on days one to three of CAPOX administration.

As dexamethasone is a glucocorticoid, one of the side effects is an increase in blood glucose levels[209]. A 10mg dose of intravenous dexamethasone has been found to increase blood glucose by 25-30%, peaking 120 minutes after administration[210]. As previously discussed (chapter 1, section 1.3.2), one of the mechanisms through which fasting may initiate a protective effect on non-cancer cells, is through a decrease in glucose and growth factors[44, 53]. This raised the question as to whether prophylactic dexamethasone use may negate the potentially protective effects of short-term fasting.

However, the exact mechanisms behind DSR are not fully understood and metabolic factors other than glucose and growth factors are likely to be involved[42, 158]. Similarly, the degree to which dexamethasone increases blood glucose if baseline levels are low, e.g., due to fasting, is also unclear. A

recent study in mice treated with doxorubicin showed that dexamethasone increased blood glucose levels and also cardiac toxicity[211]. However, fasting the mice for 24-72 hours prior to doxorubicin treatment prevented hyperglycaemia and protected mice from cardiac toxicity.

Therefore, it is unclear whether the increased blood glucose caused by dexamethasone will limit the potentially protective effect of fasting, or whether fasting will limit the potentially negative effects of dexamethasone. As it is currently standard practice to give dexamethasone to patients receiving oxaliplatin, an initial pragmatic approach is to test the introduction of a fast alongside this standard practice. Detailed data on dexamethasone administration (e.g., timing and dose) will be collected.

4.2.1.4 Measurement of sarcopenia

During protocol development, the use of Computerised Tomography (CT) to assess sarcopenia was considered. This would involve single axial images of the third lumbar (L3) level muscle mass, taken from pre-chemotherapy staging and follow-up CT scans, conducted as part of routine care in conjunction with hand grip strength measures taken at baseline and cycle 3 to assess sarcopenia[87]. However, the routine follow-up CT scans in this population group are not completed until 6-12 months post-surgery, and this length of interval between the intervention and the follow-up measurement was considered too long to provide meaningful results. So, it was decided that using hand grip strength measure alone, would be used to assess sarcopenia. The European Working Group on Sarcopenia in Older People identifies muscle strength as one of the key parameters of sarcopenia and considers muscle strength as a better predictor of adverse outcomes than muscle mass[212]. Measuring hand grip strength is a simple tool to implement in clinical research and is considered a strong predictor and accurate measure of increased functional limitations. It is therefore recommended for use in clinical settings to assess possible sarcopenia[212]. Diagnosis can then be confirmed by further testing of muscle quantity, by methods such as CT or MRI imaging. So, using hand grip strength within this feasibility trial, allows for collection of initial data on the potential issue of sarcopenia in this participant group, and will inform whether further methods of measuring sarcopenia are warranted in future trials.

4.2.2 Patient and Public Involvement (PPI)

PPI was sought through discussions with patients attending the colorectal oncology clinic at Bristol Haematology and Oncology Centre.

ES attended the oncology clinic and spoke to people in the waiting area, prior to their consultation appointments. Topics discussed included the planned type and length of fast to be used in the trial as

well as a general discussion about their own experiences of diet and appetite during chemotherapy, and what, if any, advice they had received on this topic.

PPI feedback was then used to inform decisions on the format of the fasting intervention and data collection methods used. For example, some people highlighted the importance of understanding the rationale behind fasting. They advised that if they understood the reasoning, they would be more willing and able to undertake the fast. For this reason, the Participant Information Sheet (PIS) was designed to clearly outline the rationale for fasting. PPI discussions also confirmed the importance of including hot drinks in the dietary "allowances" for the fasting arm, because people who had taken capecitabine advised that it effects the way people experience cold temperatures, and that cold water can cause throat spasms. Finally, these PPI discussions were also used to confirm that the number of additional blood samples required for the trial (n=6) is acceptable.

A Bristol Biomedical Research Centre (BRC) wide PPI group was also used for review and development of the patient literature. Feedback from this review was used to adjust the wording in the patient information sheets and the fasting instructions, to make sure the language was accessible and easy to understand. Further PPI work will be conducted, as required, to discuss any protocol alterations or issues with recruitment, retention and data collection that arise throughout the trial duration.

4.3 METHODS

SWiFT is a two-armed feasibility randomised controlled trial. 30 people scheduled to begin routine treatment with CAPOX chemotherapy for stage 2/3 colorectal cancer will be recruited and randomly allocated, in a 1:1 ratio, to either a 36 hour fast or standard dietary advice (usual care).

4.3.1 Aims and Objectives

The aim of the trial is to determine whether a 36-hour pre-chemotherapy fast is feasible in people receiving CAPOX chemotherapy for stage 2/3 colorectal cancer.

To evaluate the feasibility of the trial, the objectives are to:

- Assess the adherence to the fasting intervention
- Assess the recruitment rate to the trial
- Assess the retention rate of the trial
- Assess the acceptability and tolerability of the intervention
- Inform the outcome measures for a definitive trial

4.3.2 Participants

30 participants will be recruited from NHS hospital sites in the West of England.

4.3.2.1 Inclusion criteria

1. Aged ≥ 18 years
2. Histologically confirmed stage 2/3 colorectal cancer which is being treated with adjuvant CAPOX chemotherapy
3. Performance status ≤2
4. Able to provide written informed consent

4.3.2.2 Exclusion criteria

1. Confirmed cachexia
2. Taking medication for diabetes
3. Body mass index (BMI) ≤ 18.5 kg/m2
4. History of an eating disorder
5. Recent history of drug or alcohol abuse
6. Participating in another study that may affect the outcomes of this feasibility trial
7. Unable to speak/understand English

4.3.3 Trial Arms

4.3.3.1 Intervention

Participants randomised to the intervention arm will undertake a 36-hour water only fast, immediately prior to chemotherapy administration.

4.3.3.2 Control

Participants randomised to the control arm of the trial will receive standard dietary guidance/advice as per local standard practice. This may include verbal or written information on diet and effects of chemotherapy on appetite.

4.3.4 Sample Size

As this is a feasibility trial it was not appropriate to perform formal power calculations. Instead, a sample size of 30 was chosen based on the practicalities of conducting an early stage intervention trial within the scope of a PhD project. This sample size will also allow for estimation of parameters for potential primary outcomes in a definitive trial, helping to inform future sample size calculations[213].

4.3.5 Assignment of interventions

4.3.5.1 Randomisation

Randomisation will be completed in a 1:1 ratio using random permuted blocks. Block sizes are two, four and six. All participants are randomised using the online randomisation system, REDCap (Research Electronic Data Capture), a secure, web-based software platform designed to support data capture for research studies. A member of the site's research team will randomise the participants after obtaining written informed consent, using secure login details provided by the trial manager. REDCap shows the results of the randomisation on screen to the person randomising the participant, as well as emailing the allocation details to the database manager.

Following randomisation, participants will be given verbal and written instructions related to their allocated trial arm by a member of the trial team. These instructions will detail how and when to complete the self-reported data and, for the intervention arm, how and when to implement the fast.

4.3.5.2 Blinding

Blinding of the participant to the outcome of randomisation will not be possible, due to the nature of this intervention. However, outcome assessors of the markers of cellular metabolism (described in detail in section 4.3.6.2) will remain blind to participants allocation.

4.3.6 Outcomes

4.3.6.1 Primary outcome measures

The primary outcome measures assess the feasibility objectives of this trial. These are:

Adherence to intervention – assessed by analysis of self-reported food logs, completed by participants during the 36-hour fast. Participants will be considered to have adhered to the fast if they consume less than 14% of their Basal Metabolic Rate (BMR) requirements (kcal/day calculated using the Oxford equations for BMR[214]), in the 36 hours prior to chemotherapy administration. This equates to approximately 200 kcal per day, depending on age and gender. The aim of using a cut-off of 14% BMR is to allow participants to consume small amounts of food if they need to mitigate any side effects of fasting, whilst keeping the participant in the metabolically altered state associated with fasting. This cut off has been used in previous trials of fasting[159]. To encourage participants to only consume a small number of calories, a list of 50kcal snacks will be provided. The percentage of adherent participants will

be reported for each cycle. Reasons for non-adherence will also be recorded. Participants in the control group will also complete a self-reported food log, in the 36 hours prior to chemotherapy, to confirm that participants in this group did not follow the short-term fast.

Recruitment rates – calculated as the percentage of eligible patients recruited, as recorded in the recruitment logs at each site.

Retention rates – calculated as the number of participants who completed data collection for each fasting cycle divided by the number of participants randomised.

Acceptability and tolerability of the intervention – This will be qualitatively assessed through in depth semi-structured interviews with a subset of the trial participants.

Data completion rates – Completeness of data will be assessed for all measures at each cycle.

4.3.6.2 Secondary outcome measures

The secondary outcome measures aim to provide further information on potential outcomes of interest in a definitive trial. They will provide data on the expected range of outcome data in this patient population as well as the completeness of data collection. These measures are:

Side effects of chemotherapy – Measured using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)[215], Full Blood Count (FBC) and blood chemistry analysis (Urea and electrolytes, and liver function tests). Patient reported side effects will be collected on day 1 of each cycle prior to chemotherapy administration then as a follow-up on day 3 and day 7, to capture the transient nature of side effects. Data will also be recorded on whether participants completed their first 3 cycles of chemotherapy and reasons for dose reductions/delays/early termination if applicable.

Quality of Life – Measured using the EQ-5D-5L health related quality of life instrument[216]. This would be used to explore whether fasting, or its impact on chemotherapy side effects, increases quality of life in a definitive trial.

Haematologic toxicities – Assessed using routine FBC data collected prior to each round of chemotherapy and classified according to CTCAE criteria[217].

Markers of cellular metabolism – Measures will include glucose, insulin, IGF-I, IGF-II, IGF binding proteins (IGFBPs), -2 and -3. These will be used to study the effect of the fast on markers of cellular metabolism. They will also be considered in conjunction with self-reported dietary intake to explore adherence to the intervention, as the level of these markers would be expected to be reduced in adherent participants. Baseline samples will be collected prior to fasting, when participants attend the clinic for routine pre-chemotherapy blood tests (approx. 4 days prior to cycle 1). Follow-up samples will be collected in clinic, immediately prior to chemotherapy administration at cycles 1 and 3.

Markers of inflammation – C-reactive protein (CRP) will be measured at baseline (pre-fast) and prior to chemotherapy administration at cycles 1 and 3. In a full powered trial this would be used to explore whether fasting reduces inflammation.

Appetite – Self-reported on visual analogue scales (VAS)[218]. As chemotherapy can alter taste and appetite[219], measuring appetite is of interest to explore whether fasting negates reduced appetite through decreased treatment side effects. The VAS questionnaire is commonly used in clinical trials to measure appetite[220]. It has been found to provide acceptable levels of within-subject reliability[221] and is appropriate for use in both younger and older populations[222].

Sarcopenia – Hand grip strength will be measured three times in the dominant hand, while the participant is in a seated position, arms supported at right angles and feet on the floor. The mean of the three measures will be used to assess hand grip strength, using cut-off values defined by the European Working Group on Sarcopenia in Older People (EWGSOP) to identify low grip strength[223]. These measures will inform future trials on the prevalence of sarcopenia in this population and explore the safety of fasting in relation to this condition.

4.3.7 Study schedule

Figure 4-1 shows the flow of participants through the trial.

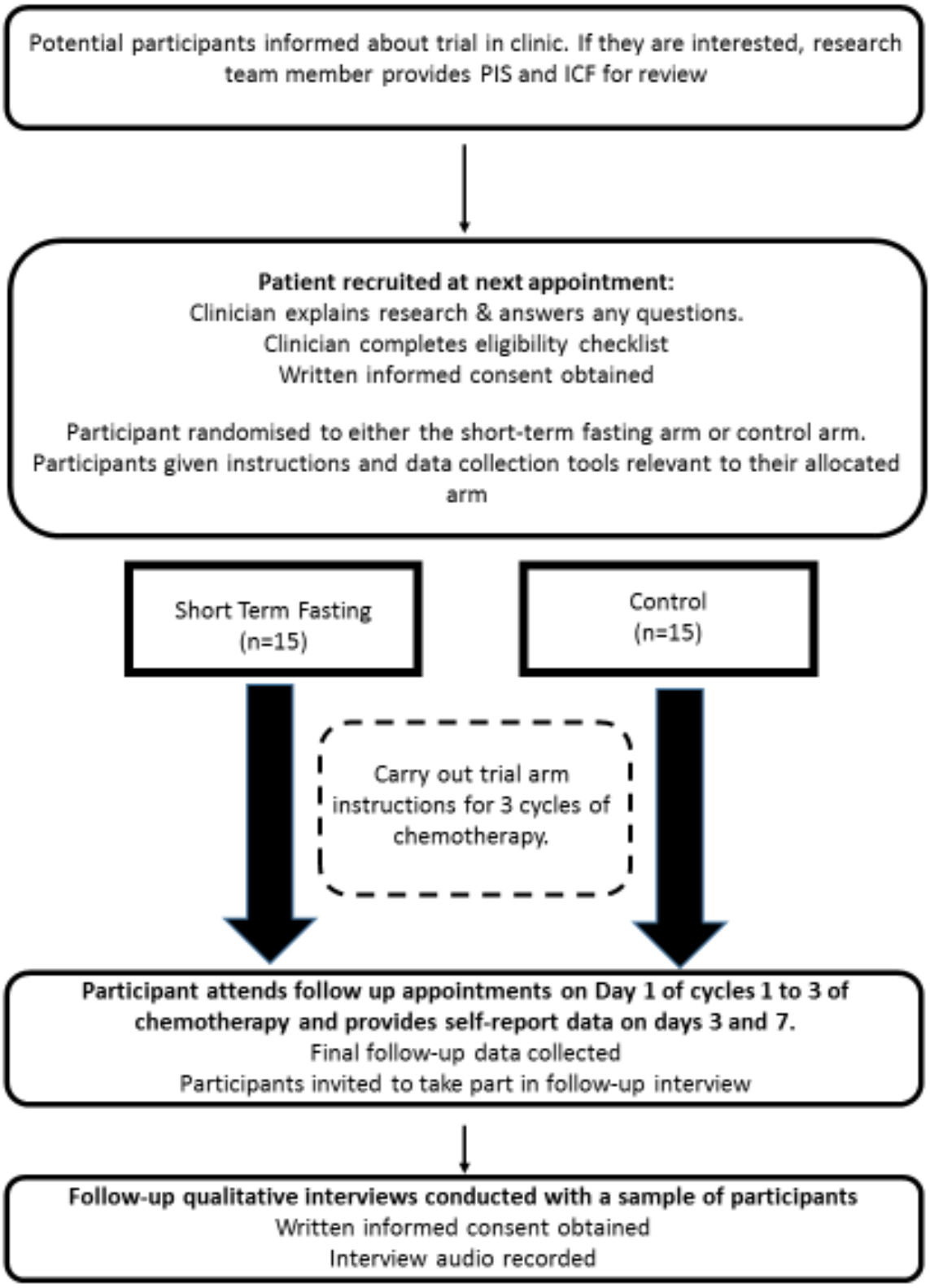

Figure 4-1 – Participant pathway
Abbreviations: PIS – Participant information sheet; ICF – Informed consent form

4.3.8 Screening and Enrolment

Potential participants will initially be identified through multidisciplinary team (MDT) meetings and screening of clinic lists by the site trial team. Potential participants will be approached by a member of their usual care team at their next routine oncology appointment following MDT. They will be provided with a verbal explanation of the trial and, if interested, will receive further details in the Patient Information Sheet (PIS) and Informed Consent Form (ICF). Potential participants will usually have a minimum of 24hours to consider participation in the trial before they are asked to confirm whether they would like to consent to take part. If a potential participant is confident that they wish to participate without this amount of time for consideration, exceptions to this may be made.

Potential participants who wish to enrol will be formally assessed for eligibility at the screening visit. The screening visit will take place at a time agreed between the site research team and potential participant. This may coincide with a routine clinic appointment such as a visit for pre-chemotherapy blood tests. However, if this is not possible, and an additional visit is required, potential participants will be reimbursed for their travel and parking expenses. The principal investigator or delegate will ensure eligibility by completing the eligibility checklist for each participant. Eligible patients will provide written informed consent, taken by the PI (or other delegated member of the site team who is trained in GCP practices). Original consent forms will be retained at the NHS site, in the Investigator Site File and copies will be sent to the BRC Nutrition Theme research team.

Eligible participants who have provided written informed consent will be randomised to either the fasting intervention arm or control arm as detailed in section 4.3.3.

4.3.9 Schedule of assessments

Table 4-1 outlines the study schedule and indicates which data will be collected at each assessment timepoint. All clinical data for the trial will be recorded on Case Report Forms (CRFs) by the clinical research team (research nurses, research assistants, principal investigator and other clinical staff trained in the trial protocol and listed on the delegation log). An example of the SWiFT “Chemotherapy Cycle 1 Day 1 visit” CRFs has been included in Appendix B. Self-report data will be recorded by the research participants electronically, though paper forms will also be provided, if the participant prefers. Data from the paper forms will be inputted into the REDCap database manually by the trial team at the BRC.

Baseline assessments will take place when the patient attends their screening visit, following successful screening and enrolment. The intervention will be implemented for the first 3 cycles of their

chemotherapy schedule. Follow-up data will be collected on days 1, 3 and 7 of each cycle. Adverse events and concomitant medication will be monitored throughout trial participation. At the end of their trial participation, each participant will resume their usual care pathway.

The end of the trial will be defined as the completion of data queries, and sample and data analysis.

*Table 4-1**: Trial schedule***

	Study Period																
	Enrolment	Baseline	Follow-up														
Timepoint	Screening	Baseline	C1 D -1	C1 D1	C1 D3	C1 D7	Pre-Cycle 2	C2 D -1	C2 D1	C2 D3	C2 D7	Pre-Cycle 3	C3 D -1	C3 D1	C3 D3	C3 D7
Enrolment:																	
Eligibility Screen	X																
Informed Consent	X																
Allocation	X																
Interventions:																	
36 hour Fast			←	→				←	→				←	→			
Assessments:																	
Demographics	X																
Height	X																
Weight	X			X					X					X			
Blood pressure	X			X					X					X			
Performance Status	X			X					X					X			
Hand Grip Strength		X												X			
FBC		X					X					X					

Timepoint	Screening	Baseline	C1 D -1	C1 D1	C1 D3	C1 D7	Pre-Cycle 2	C2 D -1	C2 D1	C2 D3	C2 D7	Pre-Cycle 3	C3 D -1	C3 D1	C3 D3	C3 D7
Blood Chemistry		X					X					X				
CRP		X		X								X		X		
Glucose		X		X								X		X		
Insulin		X		X								X		X		
Research blood sample		X		X								X		X		
Appetite		X		X	X	X			X	X	X			X	X	X
QoL		X		X	X	X			X	X	X			X	X	X
CTCAE PROM				X	X	X			X	X	X			X	X	X
Food log collection				X					X					X		
Adverse Events			Monitored during study treatment													
Concomitant Medications	X		Monitored during study treatment													

** C = Cycle; D = Day*
Other abbreviations: FBC, Full blood count; CRP, C-reactive protein; QoL, Quality of Life; CTCAE PROM, Common Terminology Criteria for Adverse Events Patient Reported Outcome Measure.

4.3.10 Qualitative Interviews

Semi-structured qualitative interviews will be conducted with a subset of the trial participants. A consecutive sampling strategy will be used, as all participants will be invited to take part once they have completed the trial. It is estimated that approximately 20 participants will be willing to take part in the interviews. Based on prior experience of conducting RCT follow-up interviews, the researchers anticipate that this will be enough to reach data saturation. However, the fact that study designs and findings are not universal, and that data saturation varies between studies must also be acknowledged, and so data saturation will be monitored during the conduct of the trial[224].

Participants will be provided with the interview specific PIS and ICF at their cycle 2 visit. They will then be invited to take part in the interview at their final research appointment by the research nurse. Details of participants who agree to take part will be notified to the BRC research team and a telephone interview will be arranged.

Informed consent will be taken prior to the interviews, including consent for the interview to be audio recorded. This will take the form of written informed consent for face-to-face interviews and audio recorded oral consent for any telephone interviews.

Interviews will be conducted by a trained qualitative researcher who is a member of the research team and is experienced in conducting qualitative research. They will follow an interview topic guide (example found in Appendices A and B), which covers topics such as experience of randomisation, tolerability of the intervention/experience of taking part as a "control" and experience of the data collection methods. It will also discuss any barriers or enabling factors that participants experienced in adhering to the fast, with the view of informing future trials of fasting interventions. However, open discussion will be promoted, and the topic guide will be continually reviewed throughout the interview process to ensure it covers any emerging topics of interest.

4.3.11 Safety Monitoring and reporting

The University of Bristol has a Service Level Agreement with University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) to ensure that all safety reporting and monitoring is managed by UHBW on behalf of the University. The study will therefore be monitored in accordance with UHBW's Monitoring Standard Operating Procedure[225]. All trial related documents will be made available on request for monitoring and audit by UHBW, the relevant Research Ethics Committee and University of Bristol. The monitoring plan has been developed and agreed by the sponsor.

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with the intervention. An event is deemed serious (SAE) if it:

1. Results in death
2. Is life threatening
3. Results in persistent or significant disability/incapacity
4. Requires hospitalisation/Prolongs a current hospitalisation
5. Results in a congenital anomaly or birth defect.

AEs will be recorded on the AE log by a member of the study team at each follow-up visit. Details on the seriousness, outcome and attribution will be recorded. Where the event is attributed to the intervention, expectedness will also be assessed. Related adverse events expected from short term fasting are: Headaches, dizziness, tiredness, hunger, weight loss and low blood pressure.

If an event is classified as serious (SAE), the principal investigator (or delegated individual) will assess the attribution and expectedness of the SAE. The SAE will be reported to the BRC research team within 24 hours of the study site's research team becoming aware of the event. The BRC team will then be responsible for further reporting to the sponsor and other regulatory bodies in accordance with standard University of Bristol and UHBW SOPs.

4.3.12 Treatment discontinuation

Treatment discontinuation will be at the discretion of the principal investigator or other attending clinician or the participant themselves. All participants who withdraw from the trial will be followed-up as per the follow-up schedule until trial completion. The exception to this will be if a participant explicitly withdraws consent for any further trial follow-up.

4.3.13 Data Management

4.3.13.1 Essential documents

A Trial Master File (TMF) will hold all essential trial documentation and will be managed by the BRC research team, under the responsibility of the Chief Investigator, at the BRC Nutrition Theme offices.

Each research site will maintain an Investigator Site File (ISF), provided to the site by the BRC Nutrition Theme. This will hold all relevant documents required for the set-up and management of the trial on site and will be the responsibility of the Principal Investigator to maintain.

Electronic Case Report Forms (eCRFs) will be completed by the study team, on RedCap, at each site for each research visit i.e., screening, enrolment, baseline and day 1 for chemotherapy cycles 1-3.

4.3.13.2 Database

Link-anonymised trial data will be stored in the REDCap online data capture system. Access to the database is via an encrypted Secure Sockets Layer (SSL) website. Participants will also upload self-report measures directly through REDCap, by accessing the website or using the REDCap mobile app. Detailed instruction on how to use the system will be provided to participants with instructions to contact the research nurse or trial manager if any difficulties occur.

REDCap data are stored in a central University of Bristol server that is managed by University of Bristol Central IT Services in line with their policies. REDCap uses Table Based username and password security, and a granular security model so users only see the data and functionality they require. An audit trail of all actions is maintained. Data validation will be completed in REDCap and any data queries resolved with the site trial team.

4.3.13.3 Archiving

All trial records will be archived on completion of the trial analysis. Anonymised data will be stored for up to 20 years on the University of Bristol's secure online Research Data Storage Facility. In accordance with the University's policy for sharing of anonymised research data, participants will be asked for their consent to make the anonymised data available to other researchers for whom this data may help facilitate the answering of their research question. Data will be deleted by secure erasing at the end of the retention period.

4.4 DATA MONITORING

A random sample of 10% of CRFs will be checked, by the BRC Nutrition Research Team, against entries within the database and with the source data, for quality purposes. The percentage checked will be increased if the error rate is deemed to be high. In addition, the first set of recruitment data collected from each site will be scrutinised.

4.5 DATA PROTECTION AND CONFIDENTIALITY

The database and randomisation system are designed to protect patient information in line with the Data Protection Act (1998) and General Data Protection Regulation (GDPR). Trial staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient

information at the trial centres (as relevant). The participants will be identified only by a patient ID number on the CRF and database. All documents will be stored securely and only accessible by trial staff and authorised personnel. Data will be collected and retained in accordance with the Data Protection Act 1998.

4.5.1 Data Analysis

4.5.1.1 Quantitative data

Rates and confidence intervals will be reported for the primary outcomes described in section 9.1. Baseline characteristics in each trial arm will be reported. Secondary outcome data will be summarised using means (standard deviations) or medians (inter-quartiles ranges) as appropriate for continuous variables, and frequencies with percentages (n, %) for categorical variables, to inform outcomes of interest and sample size calculations in future trials.

Patient Reported Outcome Measures (PROMs) will be analysed in accordance with developer guidelines[215, 216].

All quantitative data will be analysed in STATA 15[226].

4.5.1.2 Qualitative data

Audio recordings of the interviews will be transcribed verbatim by a sponsor approved transcription company. The anonymised data will be analysed using the framework method, a form of thematic analysis[227]. The framework method was chosen for this analysis because it is suited to research where a list of *a priori* questions exists which the research aims to address. In SWiFT, the aim of the qualitative methods was to further explore the acceptability and tolerability of the intervention and data collection methods used in the trial. For this purpose, an interview topic guide was developed to address these questions. The framework method allows analysis to utilise the themes set out in the topic guide, while allowing flexibility for emergent themes to also be described[228].

The full methods for conducting a thematic analysis using the framework approach is described in Chapter 5 sections 5.2.4.2.1 to 5.2.4.2.5. But in brief, a coding index, based on the interview topic guide, will be used to sort the data into themes. An inductive approach to analysis will be used, allowing emergent themes to alter the coding as the analysis progresses. Coding will be completed by a single researcher, then reviewed by a second researcher to ensure both consistency of coding and grounding in the original data. Any inconsistencies in themes or coding will be discussed and resolved between the

two researchers. This process will take place in parallel with the data collection to allow any emerging themes to be further explored in subsequent interviews. A framework matrix will then be created using participants responses to each theme. Qualitative data analysis will be assisted by Nvivo 10 software[229].

4.5.2 Biological Specimens

4.5.2.1 Routinely collected samples

All human tissue samples will be collected, processed and stored in accordance with the Human Tissue Act 2004. Baseline FBC and blood chemistry data will be collected from routine samples analysed in NHS labs as per standard practice for cycles 1 and 3. This data will be collected from participant medical records by a member of their clinical care team.

4.5.2.2 Research specific samples

As per the trial schedule (Table 4-1), blood samples taken immediately prior to chemotherapy administration at cycles 1 and 3 will be analysed within the NHS labs for serum glucose, insulin and CRP.

Additional blood samples will be collected at baseline and chemotherapy day 1 visits for cycles 1 and 3. Six millilitres of serum will be collected for analysis of IGF-I, IGF-II, IGFBP-2 and -3. Following collection, serum tubes will be inverted 8-10 times, then allowed to sit at room temperature, in the dark (e.g., within an envelope) for 30-60 minutes to clot. Samples will be centrifuged at 2500rpm for 15mins, and the serum pipetted off the top for storage. This will be aliquoted into 1.5ml eppendorf tubes (1ml per tube) for freezing (at -80°C) and storage at the NHS site until transfer to University of Bristol laboratories in the Learning & Research Building at Southmead Hospital for analysis at the end of the trial. Samples will be transferred by an NHS approved courier service, suitable for the transfer of frozen samples and signed for upon receipt at the University of Bristol labs.

4.5.3 Research Ethics Approval

This study will be conducted in accordance with Good Clinical Practice and the UK Policy Framework for Health and Social Care Research. NHS Research Ethics Committee approval for protocol version 1 dated 23rd October 2018 was received from the South West – Frenchay Research Ethics Committee on 08/01/2019 (ref 18/SW/0254).

4.5.4 Protocol Amendments

Any protocol amendments will be submitted to the Sponsor for review prior to submission for HRA and/or R&I capability and capacity review as required, in accordance with HRA guidelines. Approved versions will be tracked via version number and date and disseminated to all clinical research teams along with a summary of the changes made.

4.6 Site Selection and Trial Recruitment to date

4.6.1 Site Selection

The NIHR Bristol BRC is a research collaboration between University of Bristol and University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). UHBW was therefore involved in the early stages of protocol development and was recruited as the first study site.

Eight further potential study sites were identified and approached and asked to consider being a recruiting site for this trial. Six of these responded, with five declining to take part in the trial. Reasons given for non-participation were concerns that the fast was too long (n=2), not wanting to ask patients to fast (n=1) and concerns that it would be a difficult trial to which to recruit (n=1). One site, The Christie NHS Foundation Trust, agreed to open the trial.

Following reviews of capability and capacity at each site, The Christie NHS Foundation Trust opened to recruitment on 03/03/2020 and UHBW NHS Foundation Trust opened to recruitment on 09/03/2020. However, as described in the Covid-19 statement (page 3), the trial was subsequently suspended at both sites due to the Covid-19 coronavirus pandemic. The Christie reopened to recruitment on 22/09/2020. UHBW is yet to reopen (as of July 2021) due to decreased research staff capacity relating to COVID-19.

4.6.2 Recruitment

Original recruitment projection calculations identified that, based on the numbers of potentially eligible people being treated across the two study sites, an estimated recruitment rate of approximately 12.5% would be needed to reach the recruitment target of 30 participants within a 6-month recruitment timeframe. However, increased pressure on the NHS due to the COVID-19 pandemic, and delays in reopening the trial at UHBW, mean that trial recruitment continues to be significantly impacted. To mitigate these issues, two strategies are being followed. Firstly, a longer recruitment timeframe is being implemented. Secondly, the possibility of opening the trial at further sites is also being explored.

The inclusion flowchart, outlining recruitment to date, is shown in Figure 4-2. Nine eligible potential participants were identified at The Christie, and one consented to take part in the trial. Although based on very small numbers, this gives a current recruitment rate of 11%. The participant who consented was randomised to the intervention arm and completed all three cycles of the short-term fast. Data collection was successfully completed for each cycle and no issues were identified in the blood sampling processes. The participant also consented to take part in the follow-up telephone interview, which has been completed and audio-recorded.

Of the eight potentially eligible people who declined to take part, reasons for declining the trial that were provided to the research nurse were: indigestion issues meaning it would be difficult to fast for 36 hours (n=1), didn't want to fast (n=1), had 'a lot on their plate' and didn't want to think about a trial (n=1), stoma playing up and generally didn't want the study (n=1), not interested in going ahead with study (n=1), feeling well post-surgery, felt that dealing with chemotherapy side effects would be enough to manage (n=1), a few personal worries therefore didn't feel it was the right time to participate in a trial (n=1) and worries around weight and stoma (n=1).

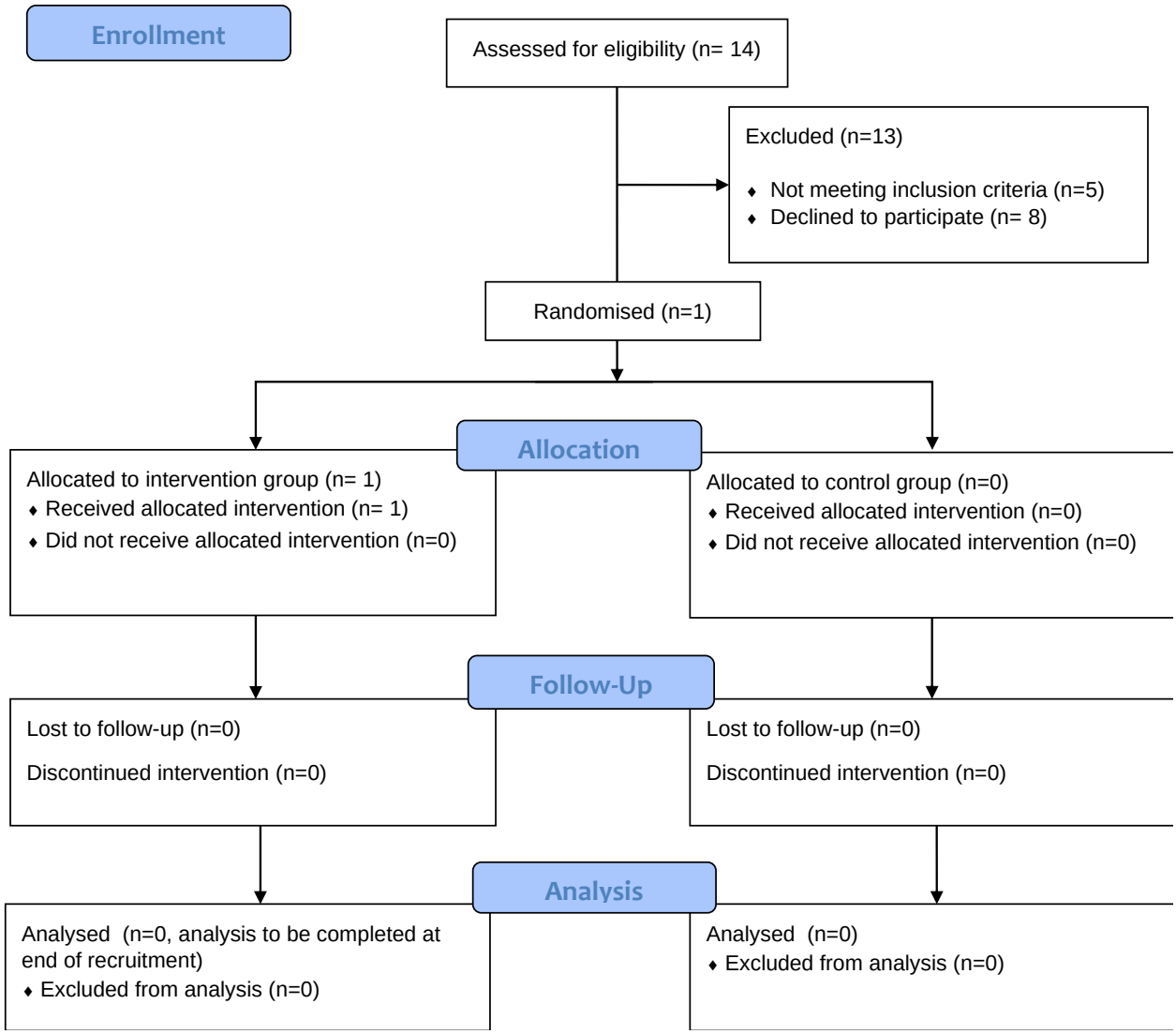

Figure 4-2: Consort flow diagram

4.7 DISCUSSION

SWiFT is the first study designed to assess the feasibility of short-term fasting in people due to undergo chemotherapy for colorectal cancer. Fasting during the treatment of cancer is an area of growing research interest, due to the findings of pre-clinical research in animal, cell line, and yeast models. Previous research has identified fasting as a potential tool for reducing the toxicities associated with cancer treatments such as chemotherapy and radiotherapy, as well as potentially improving tumour response and survival rates[59]. However, although some studies of fasting during chemotherapy in pre-clinical models have shown promising results, it is unclear how well these findings translate to humans.

Participant recruitment to this feasibility trial has been severely impacted by the COVID-19 pandemic. Directly, it caused a suspension of the trial at both recruiting sites, delaying the start of the trial. The subsequent reduced capacity at sites (due to added pressures on NHS staff time resulting from the COVID-19 pandemic) means that UHBW has been unable to reopen at the time of writing, while at The Christie, the site has reopened but with the *proviso* from their Research and Development department that recruitment may continue to be impacted.

In addition to this, recruitment has likely been impacted indirectly due to the broader implications of COVID-19 on cancer services. For example, from March 2020, the UK national bowel screening programme was suspended resulting in a 90% reduction in the number of colonoscopies in April 2020[230]. The impact of this has persisted beyond the initial national lockdown, as the number of people waiting over 6 weeks for an endoscopy in August 2020 was still nine times higher than it was in August of the previous year. This reduction in screening and diagnostic tests can be seen to impact treatment figures across the UK, with 22% fewer patients starting cancer treatment for any cancer type in August 2020 compared to August 2019[230]. It is likely then, that recruitment to SWIFT has been taking place in an environment where there is a reduced pool of potentially eligible patients to screen and approach for the trial. There is an acknowledgement that there will continue to be a disruption in cancer services while the recovery process continues, and this will therefore impact clinical trial conduct going forward.

It is also possible that certain aspects of the intervention itself have limited recruitment. For example, it is possible that this population have additional compounding issues that would limit their interest in dietary interventions, specifically. One previous study of a physical activity and dietary intervention in colorectal cancer survivors identified time following surgery and chronic diarrhoea as barriers to

recruitment and adherence [231]. The study authors reported that many participants had ongoing health-related issues following surgery, including diarrhoea and some also had pain and fatigue. It is therefore possible that additional anxieties related to food intake at this time, due to surgical treatment for colorectal cancer, could limit recruitment. Continued data collection from the screening logs for the duration of the trial should go some way to answering this question.

At the time of writing, one participant, randomised to the intervention arm, has completed trial follow-up. No conclusions regarding the feasibility of recruiting to the trial or adhering to the intervention can therefore be drawn. As the samples will be analysed at the end of the trial, it is also not yet possible to explore the impact of the fasting on markers of cellular metabolism. However, no issues with data collection processes were identified with the first participant, as data collection from each assessment timepoint was completed. A follow-up telephone interview was also conducted with the first participant, during which the participant reported that they were able to adhere to the fast for each of the three cycles. Qualitative data is yet to be fully analysed as only one interview has been conducted.

4.7.1 Implications for further research

A high proportion of potential study sites declined to open SWiFT, with two main concerns cited; the ability to recruit (which would therefore impact on recruitment targets within a Trust) and concerns over asking their patients to fast. Thus, the generation of preliminary feasibility and safety data from early-stage trials such as SWiFT is needed, as it could provide assurances to healthcare practitioners on both the ability to recruit and on the safety of the intervention. In SWiFT, data on recruitment and adverse event reporting will address both of these aspects in relation to future short-term fasting interventions. Potential reasons for the high decline rate among sites are discussed further in section 6.2.1.

The proportion of eligible people who declined to take part in SWiFT has also been high, to date, with one out of nine people who were approached consenting to the trial. However, this observation is based on small numbers, collected from one study site. The average rate of participation in colorectal studies registered with the National Cancer Research Network was 14.8% between 2001 and 2008. Recruitment to SWiFT could therefore be considered to be similar to or lower than average, assuming a similar rate of recruitment ensues. A range of reasons for declining to take part were provided, with no singular

feature of the trial being attributed to why people declined. Although concerns were raised by sites who were approached to open the trial regarding length of fast, this was not specifically highlighted by potentially eligible participants. It is not possible to compare recruitment to SWiFT to previous trials of fasting and fasting mimicking diets, as the recruitment rates have not been reported in previous trials[65, 195]. The recruitment rate, and reasons for declining the trial will continue to be monitored within SWiFT through data provided in screening logs from the research sites. This will allow any emerging patterns to be monitored, reported and, where possible, addressed to aim to improve recruitment.

If recruitment to SWiFT remains low, future studies could include the expansion of the study population or alteration of the intervention itself. For example, as discussed in chapter one, the potential for energy restriction to reduce cellular damage caused by radiotherapy is also of interest. As seen in chapter three, however, this has mostly been studied in the context of ketogenic diets, to date. Broadening the intervention of short-term fasting to this population in future trials, could therefore provide an increased pool and provide important feasibility data on this group. If the type or length of fast is found to be unacceptable, or to lead to a low recruitment rate, alternatives such as the fasting mimicking diet described in chapter 1 (section 1.4.3), could be implemented in its place. This form of diet comprises a very low-calorie diet consumed over 5 days and aims to alleviate some of the barriers to total energy restriction.

Amendments to the protocol could also be made to aim to collect more in-depth information about why people have declined the trial. For example, using qualitative interviews with people who decline the trial, may ascertain reasons not identified by the study team when completing the screening logs.

As well as using further qualitative methods to explore recruitment barriers from participants themselves, recruitment interventions aimed at those recruiting to the trial could also play a role. Qualitative research has been successfully used to identify key barriers to recruitment in RCTs of complex interventions[138]. Based on the findings identified through qualitative research, training programmes for those recruiting to the trial can be developed to target the “pain points” that have been identified as deterrents for recruitment. For example, the QuinteT (Qualitative Research Integrated in Trials) Recruitment Intervention (QRI) has been used to successfully improve recruitment to RCTs. The QRI involves two phases. The first includes in-depth interviews with trial recruiters and audio recording recruitment discussions, to fully understand the trial recruitment process. The findings from this host of qualitative work are fed back to the trial investigators and managers so that, in the second phase,

strategies to combat identified issues can be implemented[136]. For example, previous qualitative interventions have found that potential participants often find RCT concepts difficult to understand and that recruiters may struggle with the concept of uncertainty between trial arms[138]. So, training and provision of support strategies could be used in the second phase of the QRI to help overcome these issues. This could include provision of study-specific "tips and guidance documents" to investigators, with recommendations for how to structure consultations with potential participants and how to explain common trial concepts such as randomisation[232]. However, this level of intervention is not required for all complex interventions and would increase costs, and potentially timelines for the trial. It may therefore not be possible within the scope of the current trial. However, the current trial could identify whether such interventions may be required in future RCTs.

Although the current study has not been completed at the time of writing this thesis, it will continue to be run, as described in this protocol, by the Peri-treatment Workstream team in the Nutrition Theme of the BRC. Should the results from this study show that the trial is feasible, and that it may result in benefit to participants, data will be used in future grant applications for a larger trial.

4.7.2 Strengths and limitations

SWiFT will provide data on the feasibility of conducting a fasting intervention at the time of chemotherapy in people undergoing treatment for colorectal cancer, a population previously unstudied in this area. The embedded interview study will also allow for a qualitative assessment of patient experiences of the acceptability and tolerability of the intervention and data collection methods used in the trial. It will use validated questionnaires to collect data on treatment side effects experienced by trial participants, using patient reported outcome measures. This will give a patient-centred view of adverse events experienced during the trial.

SWiFT also uses a pragmatic design which closely follows the usual clinical pathway for people receiving CAPOX for colorectal cancer. As such it aims to limit the burden of the trial on participants, by removing the need for additional visits to site, and also on the site study team, by limiting the number of additional assessments and procedures that need to be completed. Although it will have a small sample size and will not be powered to determine effects of the fast on treatment toxicities, collecting data on secondary outcomes such as chemotherapy side effects and markers of cellular metabolism will help to inform sample size calculations in future trials.

One of the main limitations of this study is that it will be difficult to determine the actual recruitment rate, due to the indirect effects of COVID-19 on cancer services discussed previously. This is of particular concern as recruitment rates are a primary objective to assess feasibility of the trial.

A further limitation is that underlying reasons for participants declining to take part may be missed through only using screening log data. For example, one previous trial of ketogenic diets in people with glioblastoma conducted qualitative interviews with people who declined to take part. The interviews identified that quality of life was an important factor in the decision-making process for taking part in the trial, and that this facet of declining the trial was not picked up in data from screening logs[192]. If decline rates remain high in SWiFT, further qualitative work may be warranted to fully understand the reasons for declining participation in the trial.

4.7.3 Summary

SWiFT is a feasibility RCT of short-term fasting prior to CAPOX chemotherapy for colorectal cancer. It aims to provide data on the feasibility of recruiting to a trial of short-term fasting prior to chemotherapy and on participant adherence to the intervention, and any adverse events that are associated with the fast. It will also provide preliminary data on the effect of the intervention on markers of cellular metabolism and treatment-related adverse events, which can be used in sample size calculations for any future, definitive trials. Delays to recruitment due to the COVID-19 pandemic mean that no conclusions can be drawn yet regarding the feasibility of the trial. However, the trial remains open, and the findings will show whether a large trial is feasible or if changes to the protocol are needed to resolve any issues that may be identified.

Key Messages

1. SWiFT is the first study to assess the feasibility of short-term fasting in people due to undergo chemotherapy for colorectal cancer.
2. The aim of the trial is to determine whether a trial of a 36-hour pre-chemotherapy fast is feasible in people receiving CAPOX chemotherapy for stage 2/3 colorectal cancer.
3. Although recruitment to SWiFT was delayed due to the COVID-19 pandemic, the trial remains open, with recruitment ongoing.
4. To date, one participant has completed the trial and data collection was successfully completed for each trial assessment timepoint

5. The current recruitment rate is low, but is based on small numbers to date and only one study site. Recruitment will continue to be monitored and the protocol amended, if required.

Chapter 5 THE B-AHEAD 2 TRIAL OF INTERMITTENT ENERGY RESTRICTION COMPARED TO CONTINUOUS ENERGY RESTRICTION IN WOMEN RECEIVING CHEMOTHERAPY FOR BREAST CANCER – A MIXED METHODS SYNTHESIS

5.1 BACKGROUND

One of the original aims for this thesis was to conduct a nested qualitative study within the SWiFT trial to assess the acceptability and tolerability of the dietary intervention. However, as described in Chapter 4, the SWiFT trial was paused to recruitment due to the Covid-19 pandemic. As an alternative, an existing, previously unanalysed, dataset from a trial of dietary restriction in women being treated for early breast cancer was used for the current analysis. The data were collected as part of the "Breast activity and healthy eating after diagnosis – 2" trial, which was a trial conducted between May 2013 and September 2014 by University Hospital of South Manchester (UK) The protocol was not published as a manuscript, but the trial is registered at: ISRCTN04156504[233]. The trial design is described in section 5.2.1. The aim of the analysis for this thesis was to explore the feasibility of adhering to energy restriction diets at the time of chemotherapy, focusing on behaviour change and participant experience, and to identify facilitators of and barriers to the intervention.

Trial recruitment and data collection were completed by University Hospital of South Manchester, who provided cleaned datasets for this analysis. As part of this thesis, a data analysis plan was developed and the data analysis and interpretation of results are detailed in this chapter. ES developed the data analysis plan, with input from CA, CP, GH, AN, MH and a medical statistician. ES developed the coding for the quantitative analysis, with review by a medical statistician, and ran the analysis. ES was responsible for the presentation, interpretation, and discussion of the results, with review and input from CA, CP, GH, AN and MH. The data analysis and interpretation of results are detailed in this chapter.

"Breast activity and healthy eating after diagnosis – 2, During chemotherapy for early breast cancer" (B-AHEAD 2) was a feasibility RCT comparing a continuous energy restriction (CER) diet to an intermittent energy restriction (IER) diet in women receiving chemotherapy for stage 1-3 breast cancer. Being overweight at the time of breast cancer diagnosis and weight gain during chemotherapy increases the

risk of breast cancer recurrence and death[234]. Previous research by University Hospital of South Manchester has found that IER is equivalent/superior to CER for general weight control in women with a family history of breast cancer[235]. And, as discussed in Chapter 1, IER at the time of cancer treatment may have the additional benefit of reducing toxicity during cancer treatment. Therefore, the B-AHEAD 2 RCT was conducted to assess the effects of these interventions on weight control and chemotherapy toxicity during chemotherapy for breast cancer.

This chapter will describe the overall trial design used in the B-AHEAD 2 trial (section 5.2.1) and the methods employed in this specific analysis of two secondary data sets from the trial (5.2.2). These data will be used to explore the feasibility of adhering to energy restriction diets at the time of chemotherapy, with a focus on behaviour change and participant experience.

5.2 METHODS

5.2.1 The B-AHEAD 2 trial

5.2.1.1 Aims and outcome measures in the main trial

The overall aim of the trial was to assess whether IER was more effective than CER in preventing weight gain in normal weight women and promoting weight loss in overweight women, during chemotherapy for early breast cancer.

The primary outcomes of the trial were relative changes in weight, body fat and fat free mass (assessed by DXA) between the IER and comparison CER group over the course of chemotherapy treatment. Sample size calculations for the trial estimated that 66 women in each group would provide 90% power to detect differences in a clinically significant change in body fat from baseline to 4.5-6.0 months between the IER and CER groups of ≥2.0kg.

The secondary outcomes included relative changes in serum markers of breast cancer and cardiovascular disease, quality of life, self-reported chemotherapy toxicity, adherence using 7-day diet diaries and behaviour change scales.

A qualitative sub-study was also conducted with a subset of women from both intervention groups. The aim of the qualitative study was to explore participant views on factors which either facilitated or limited adherence to IER or CER, to identify strategies which may help to improve adherence to dietary interventions.

5.2.1.1 Participants

Participants were deemed eligible if they were female, aged ≥18 years, had a blood haemoglobin level >110 g/l and a BMI >19 kg/m2.

Participants were excluded if they had metastatic disease, chemotherapy for breast or other cancers within the previous two years, physical or psychiatric conditions that could limit adherence or were taking medication for diabetes.

5.2.1.2 Recruitment

The trial received research ethics approval from NRES Committee North West - Greater Manchester West (reference 12/NW/0230) and written informed consent was obtained from all participants. Participants were recruited from 10 breast units in the Greater Manchester Clinical Research Network, UK between May 2013 and September 2014.

5.2.1.3 Trial arms

Participants were randomised, using a computer minimisation programme to either:

1. IER (2 days/week) plus exercise weight control intervention or
2. Daily CER plus exercise weight control intervention.

Randomisation was stratified by:

1. Whether women were scheduled to receive adjuvant or neoadjuvant chemotherapy.
2. Whether women were normal weight or overweight/obese.
3. Whether women were pre- (and peri) or post-menopausal.

5.2.1.3.1 Energy restricted diets

Participants followed the allocated diet for the duration of their chemotherapy treatment (4.5-6 months, depending on chemotherapy regimen).

Two forms of energy restricted diets were compared in the B-AHEAD 2 trial; IER and CER. Both diets were designed to prevent weight gain in normal weight women and to promote gradual weight loss of 0.5 –1kg per week amongst overweight or obese women. In order to achieve this, normal weight women (defined as a BMI 19-24.9 kg/m2), in both groups, were prescribed a diet which met their estimated energy requirements, whilst overweight/obese women (defined as a BMI ≥25 kg/m2) were prescribed a 25% energy restricted diet. The baseline energy requirements were calculated from

estimated basal metabolic rate, based on Henry equations[236] multiplied by their activity levels, as reported in the baseline physical activity questionnaire (IPAQ)[237].

Within the IER group, this comprised two restricted days where women followed a low energy diet consisting of <50g carbohydrate / day and *ad lib* protein, which self-limits to approximately 800-1000 kcal/day. On restricted days, participants were advised to only consume:

- Protein foods
- Healthy fats
- Three portions of dairy
- One portion of low carbohydrate fruit
- Five portions of low carbohydrate vegetables or salad
- At least two litres of low-calorie drinks

The two restricted days were undertaken on the two days immediately prior to chemotherapy during the weeks of chemotherapy administration. On the remaining five days of the week, women followed a Mediterranean diet, tailored to achieve their target of weight maintenance or loss, taking into account their estimated energy requirements and their anticipated intake on the restricted days.

Within the CER group, the diet comprised a Mediterranean diet, with a daily 25% energy reduction, based on their estimated energy requirements, for those in the overweight/obese category.

The Mediterranean diet prescribed in both arms of the trial was based on wholegrain carbohydrate sources, monounsaturated fat sources such as olive oil, low saturated fat intake, and included fruits (two portions per day), vegetables (five portions per day), low fat dairy (three portions per day) and oily fish.

Meal recipes and snack ideas were provided to both arms as well as a guide on portion sizes and personalised carbohydrate and protein intake requirements.

5.2.1.3.2 Physical activity

Women were advised to follow published physical activity guidelines for people receiving adjuvant chemotherapy for breast cancer[238]. This involved gradually increasing the frequency and intensity of exercise to aim to take 2.5 hours (5 x 30 minutes) of moderate activity/week, at 60–80% maximum heart rate. All participants were provided with pedometers (model: Omron HJ 113) to monitor their exercise with the aim of promoting adherence to guidelines.

5.2.1.4 Behavioural change intervention

The B-AHEAD-2 interventions were not based on a single behaviour change theory, instead, three behavioural change concepts were targeted and measured in the B-AHEAD 2 Trial. These were self-efficacy, habit formation and eating style/behaviour. The scales and methods which were used to measure these concepts are described in section 5.2.3.2. One of the aims of the trial was to use the responses to the scales to understand the processes of behaviour change and adherence amongst women receiving chemotherapy, and to identify if future interventions can be designed to overcome any identified barriers.

During intervention delivery, participants in each group received face-to-face, tailored dietary advice from study dietitians at the start of the trial. This was followed by fortnightly telephone calls from the dietitians to check compliance and identify any problems encountered when following the diets. These contacts used established behaviour change techniques such as goal setting and self-monitoring. Individual goals and recommendations were discussed in order to reinforce their behavioural goals and address any issues that arose throughout the trial. Women were then mailed an individualised summary of key motivational, behavioural and diet issues identified during the phone call.

As well as the advice on individualised goal setting and monitoring, women also received standard fortnightly mailings which covered further information on IER or CER, weight management, diet, physical activity and chemotherapy. They also covered common behavioural change concepts such as self-efficacy and gaining control of eating habits. Details of the information covered in the mailings and dietitian contact are described in further detail in section 5.2.1.4.1 to 5.2.1.4.3 below.

5.2.1.4.1 Self-efficacy

Self-efficacy describes a person's belief in their ability to influence aspects of their lives (e.g. diet and exercise) through their own action[239]. Self-efficacy has been shown to influence how well people are able to motivate themselves to incite change and also how resilient they are when trying to achieve the goals that they have set for themselves[240]. Within dietary behaviour change research, it has been shown that self-efficacy can be increased through behavioural change intervention strategies which aim to improve stress management, promote self-monitoring of dietary behaviours and reviewing dietary goals [241]. Improving dietary self-efficacy can, in turn, be an effective way to incite behaviour change[242].

Within the B-AHEAD 2 trial, women were encouraged to set and monitor dietary goals throughout the intervention, aided by the regular contacts with the dietitian. Participants were encouraged to set and record goals using the SMART acronym (Specific, Measurable, Achievable, Realistic and Timed). One example given was to 'lose 1-2lb each week for the next 6 weeks.' Participants were also provided with practical steps to take in the event of lapsing on their goals e.g. to "learn" by considering what had happened to lead to a lapse in their goal and to "plan" to put their plan back into action. By supporting participants in this way, the trial team aimed to maintain or improve participant self-efficacy, with the ultimate goal of maximising adherence to the diets.

5.2.1.4.2 Habit formation

Habit formation is one of the strongest predictors of eating behaviour[243] and is understood to contribute to maintenance of behaviour change[244]. A habitual behaviour is formed when the behaviour is repeated in a consistent setting or context. This leads to the activation of a learned association between the context and the action, inciting an automatic response to the contextual cues[245, 246]. As habit formation provides a mechanism for establishing new behaviours, habit formation and automaticity are outcomes of interest in dietary and physical activity interventions and can be used to assess intervention success[247]. Thus, exploring whether either intervention resulted in habit formation within B-AHEAD 2 provides the opportunity to assess whether the interventions were successful at inciting behaviour change.

5.2.1.4.3 Eating style

Previous research has identified that people who are overweight or obese are more likely to exhibit particular eating styles. These are i) an over responsiveness to external food cues and an under responsiveness to internal cues of hunger and satiety (together referred to as externality) and ii) a propensity to eat more under stress (referred to as emotionally triggered eating)[248]. Dietary interventions which modify these eating behaviours therefore have the potential to reduce these disordered eating styles which are associated with being overweight. This is of particular interest in the chemotherapy setting, where weight gain can occur in both normal and overweight women with increased energy intakes and decreased energy expenditure, due to psychosocial and anxiety related factors[249].

Within the B-AHEAD 2 trial, participants were monitored by the study team, through the regular contacts with the dietitians, to identify any issues with anxiety or other psychological issues arising from their chemotherapy. Any psychological issues were dealt with appropriately by referral to relevant

cancer support services. Participants were also provided with educational literature, via the fortnightly mailings, on how chemotherapy can cause stress and fatigue, with tips on how to prevent and manage stress associated with cancer treatment. Specifically, these mailings advised on how stress can impact diet by causing them to turn to sugary or unhealthy snacks, with guidelines on how to avoid these common pitfalls e.g., eating at regular times, avoiding reliance on caffeine or alcohol, and following the targets and guidelines set out within their specific diet. Literature was also provided, via the mailings from the dietitians, on how to gain control of eating habits, focusing on aspects such as dealing with cravings, and how to avoid using food as a reward system. Participants' eating style was measured at baseline and end of trial so that any changes in eating style could be monitored and assessed.

5.2.1.5 Data collection

5.2.1.5.1 Quantitative data

Participant characteristics and baseline behaviour data were collected in clinic prior to commencement of either adjuvant or neoadjuvant chemotherapy. Baseline characteristics included age, BMI, menopausal status, ethnicity, index of multiple deprivation, smoking status, chemotherapy regimen, tumour grade and whether participants have children at home.

Follow-up data were collected at the end of the trial, three weeks after the final chemotherapy cycle. This comprised paper questionnaires for the behaviour change data and Tanita scale measurements for weight data, completed in clinic.

Dietary intake data, which were used to assess adherence, were collected for one week at baseline, for 3 weeks during the trial at cycle 3 or 4 and for one week at the end of the trial (3 weeks post chemotherapy) using self-reported 7-day food diaries.

5.2.1.5.2 Qualitative data

Qualitative data were collected via in-depth individual interviews with a subset of trial participants. Participants who expressed an interest in taking part in the qualitative sub-study were invited to take part in semi-structured interviews, and interviews continued until the qualitative researchers considered data saturation had been reached. A purposive sampling technique was also employed, to ensure participants from both intervention groups were included. To understand longer-term behavioural maintenance in this group, interview participants were also invited to attend a second interview, 6 months later.

The interview topic guides used for qualitative data collection are included as appendices E and F. The interviews were conducted, transcribed and anonymised by the B-AHEAD 2 trial team and anonymised transcripts were provided for this analysis.

5.2.2 Data analysis

This section describes the analysis, conducted for this thesis, of two datasets from the B-AHEAD 2 trial. These are:

1. Quantitative data: Questionnaire data which comprised four validated motivational, health belief, and self-efficacy scales for 169 participants and
2. Qualitative data: Transcripts from semi-structured interviews for 13 participants

The overall aim of the analyses was to explore the feasibility of adhering to energy restriction diets at the time of chemotherapy, focusing on behaviour change and participant experience, to identify facilitators of the intervention and whether future interventions could be tailored to overcome identified barriers. It also aimed to compare the two diets, to identify whether differences in factors associated with adherence existed between the two intervention groups.

Analysis of the quantitative data was used to explore the relationship between some common behavioural change concepts and adherence to, and outcomes of, the diets. The data were used to assess whether key behaviour change concepts predict adherence to the dietary interventions, and whether these predictors differ between the IER and CER groups in the trial.

Analysis of the qualitative data was used to further explore participant experience of following the IER and CER diets and aimed to identify whether differences in participant experiences of adherence exist between the two diets.

Finally, results from these two analyses were integrated in a mixed methods design, allowing interpretation and reporting of the two methods in combination. Therefore, methods used in this analysis of the B-AHEAD 2 data include quantitative and qualitative analyses and a mixed method synthesis. Each component is described in detail below.

5.2.3 Quantitative Methods

Participants completed paper questionnaires which included four validated motivational, health belief, and self-efficacy scales. Questionnaires were completed in clinic at baseline (prior to chemotherapy and

the start of the dietary intervention) and at follow-up (three weeks after final chemotherapy). The questionnaires are described in section 5.2.3.2 below and are included as appendices C and D.

5.2.3.1 Aim

The questionnaires capture some of the key concepts used in the B-AHEAD 2 behavioural change interventions which have been described in section 5.2.1.4. The aim of this analysis was to assess the behavioural factors which facilitate or reduce adherence to the diets, and to identify whether differences in these factors existed between the diets. Comparing behaviour concept scores between the intervention groups will also help to explore whether differences exist between the two diets, in terms of predictors of adherence and the intervention's ability to alter behaviour. Further understanding of factors that affect adherence to, and outcomes of, behavioural change interventions could inform the development of future interventions in cancer survivors to improve effectiveness of these interventions [250].

Five research questions were identified to address this aim:

1. Do either of the interventions alter behavioural change concept scores from baseline to end of trial?
2. Is there a difference in behavioural change concept scores between intervention groups at the end of the trial?
3. Do baseline behavioural concepts (self-efficacy, habit formation and eating style) predict adherence to IER or CER in women receiving chemotherapy for breast cancer?
4. Do baseline behavioural concepts (self-efficacy, habit formation and eating style) predict weight change in either the IER or CER groups?
5. Are changes in in behavioural concept scores associated with either adherence or weight change in either the IER or CER group?

5.2.3.2 Behaviour change data

5.2.3.2.1 Self-efficacy

Two scales were used to measure self-efficacy. The first measured whether women felt that their weight and breast cancer prognosis was in their control, based on the obesity cognition questionnaire by Larsen *et al*[251]. The questionnaire was developed by the lead trial team to provide measures of two specific

aspects of self-efficacy in relation to diet during chemotherapy; perceived behavioural control and perceived benefit. It is a 6-item scale with responses made on a 5-point Likert scale ranging from 1 (strongly agree) to 5 (strongly disagree). Questions were positively phrased with the exception of two questions which were negatively phrased. The answers to these negatively phrased questions were recoded so that high values indicate a high degree of self-efficacy and locus of control. As per the guidelines from the questionnaire developers, mean scores were calculated and questionnaires with more than two responses missing were excluded from analyses.

The second scale measured self-efficacy for carrying out weight control behaviours**.** This scale was adapted from a self-efficacy of dieting questionnaire which describes participant confidence in dieting under certain conditions[252].The original scale developed by Clarke et al consisted of 20 items covering 5 sub-scales: negative emotions, availability, social pressure, physical discomfort and positive activities[252]. Responses were made on a 5-point Likert scale ranging from 1 (not at all confident) to 5 (extremely confident). As per the developer guidelines, scale scores were derived by summing the items within each of the five subscales, and as a single general scale, where scores from the five subscales were summed[252]. Again, a higher score denotes a higher level of self-efficacy. Subscales with more than one missing item were excluded from analyses, and the corresponding general self-efficacy scale was also excluded.

5.2.3.2.2 Habit and automaticity

This scale is based on the self-report habit index[244]. Participants answered 4 questions on the degree to which “watching their diet” was habitual and 4 questions on the degree to which exercising was habitual. Responses were made on a 7-point Likert scale ranging from 1 (agree) to 7 (disagree). Scores from reversed questions were recoded so that high values indicate strong habits and a mean score was calculated for each behaviour, as per the questionnaire design. Questionnaires with more than one response missing for either behaviour were excluded from analyses.

5.2.3.2.3 Eating style

The Dutch eating behaviour questionnaire describes eating styles as either restrained or cued by external or emotional factors[253]. It is a 33-item scale which covers 3 dimensions of eating behaviour: cognitive restraint (10 items), externality (10 items) and emotionality (13 items). Responses were made on a 5-point Likert scale ranging from 1 (never) to 5 (almost always). The scale was scored as per the questionnaire design, and mean scores were calculated for each dimension. Those with more than three

missing responses in the restraint and externality scales, and more than 4 missing responses in the emotionality scale, were excluded.

5.2.3.3 Dietary data

Dietary intakes were recorded using self-reported 7-day diet diaries completed at baseline (1 x 7-day diary), during the trial (three consecutive 7-day diaries) and at three weeks after the final chemotherapy cycle (i.e., end of the trial period; 1 x 7-day diary).

Daily energy (kcal) intake was derived from the diet diaries using WISP V3 (Tinuviel Software, UK) by the B-AHEAD 2 trial team. The WISP nutrient database uses data from the UK Nutrient Databank[254].

5.2.3.4 Weight change data

Weight was measured in clinic by Tanita scales (MC-180MA Tanita scale, Tanita Europe, Amsterdam, The Netherlands), at baseline and end-of trial.

5.2.3.5 Statistical analysis

All quantitative data were analysed in STATA 16[226].

Descriptive statistics were used to summarise the baseline characteristics using means and standard deviations or medians and inter-quartiles ranges, as appropriate, for continuous variables, and frequencies with percentages for categorical variables. Baseline characteristics of those with complete adherence and weight data were compared to those with missing data for those variables.

Four sets of analyses were conducted in order to answer the research questions described in section 1.2.3.1.

5.2.3.5.1 Analysis 1: Assess the effect of the intervention on behaviour change scores (question 1).

Questionnaire scales were scored according to their design, as described above.

To assess whether either intervention altered behaviour change scores, the scores from each of the scales described above were compared from baseline and end of trial for each intervention group, using a Paired t-test or Wilcoxon test, as appropriate.

To compare the effect of the interventions on behaviour change concepts between the groups, a Mann-Whitney test was used to compare the scores between the intervention groups at the end of the trial.

5.2.3.5.2 Analysis 2: Comparing adherence between the intervention groups (question 2).

Adherence was assessed using the self-reported energy intake recorded in the 7-day food diaries completed at the end of the trial, while participants were still following the diets. The diaries completed at this timepoint were used to assess adherence as they had the lowest level of missing data of those completed in the middle the intervention.

Adherence to both interventions was assessed using the energy requirement calculated for the diet prescription defined in section 5.2.1.3.1. Normal weight women were asked to meet their estimated energy requirement. Overweight women were given a target corresponding to 75% of their estimated energy requirement. For both normal weight women and overweight women, a 5% margin of error was applied when defining adherence. A 5% cut-off was chosen to allow for some error in reporting, without affecting their ability to reach weight loss/maintenance target. This definition of adherence provides a binary variable for adherence that is comparable between the intervention groups. For women in the IER group, as energy intake varied on restricted days compared to the remaining five days of each week, adherence was calculated over a whole week. Participants were considered to have "missing" adherence data if at least one day of self-reported diet diaries were not completed. Logistic regression was used to compare adherence between the two interventions.

Self-reported 7-day food diaries were also collected for three consecutive weeks during cycle 3 or 4 of the participants chemotherapy regimen. Intakes recorded in these diaries were summarised to provide a description of adherence across one full cycle of chemotherapy and were compared between intervention groups. Understanding adherence across one cycle of chemotherapy is of interest as adherence may vary due to fluctuations in treatment toxicities and also its effects on appetite.

5.2.3.5.3 Analysis 3: Assess whether baseline behavioural change scores (self-efficacy, habit formation and eating style) predict adherence or weight change in each group (questions 3 and 4).

Evidence from previous research was used to identify potential confounders to include in analyses. Age, weight and socioeconomic status have previously been found to act as predictors of adherence to dietary interventions[255, 256]. As they may confound the association between behaviour scores and adherence, each of the following logistic regression models were run as unadjusted models initially, then adjusted for baseline age, weight, and index of multiple deprivation.

Firstly, to assess whether baseline behaviour scores predict adherence to the intervention in each group, the association of each behavioural concept was tested for each intervention group separately.

Logistic regression was used to test for associations between baseline behavioural change scores and adherence. The unadjusted and adjusted results are presented as odds ratios. However, as the outcome (adherence) is common, the odds should not be interpreted as risk ratios, as this would overestimate associations. As such, odds ratios provided should be interpreted with caution.

Secondly, weight change from baseline to end of trial (three weeks after final chemotherapy administration) was calculated and summarised using mean (standard deviation) for each group. Linear regression was then used to assess whether baseline behaviour change scores predict weight change in each intervention group. Results are presented for the unadjusted model, and also after adjusting for potential confounders.

As 35% of participants were in the normal weight category at the start of the trial and were therefore aiming to maintain rather than lose weight, stratified analyses were also conducted to assess whether associations between baseline behaviour concept score and weight change differed between those who were normal weight and those who were overweight/obese at baseline.

5.2.3.5.4 Analysis 4: Assess whether change in behavioural change scores (self-efficacy, habit formation and eating style) from baseline to end of trial are associated with adherence or weight change in each group (question 5).

To understand whether the behaviour change effected through the intervention influenced adherence, the difference in behaviour scores between baseline and end of trial were calculated. A logistic regression model was then used to estimate the effect of the change in behaviour scores on adherence. Odds ratios from the unadjusted and adjusted models are provided.

This method was repeated to assess whether change in behaviour scores from baseline to end of trial was associated with weight change in unadjusted or adjusted models. Again, a stratified analysis was also conducted to assess whether associations between change in behaviour score and weight change differed between the normal weight and overweight/obese groups.

5.2.4 Qualitative Methods

5.2.4.1 Aim

The aim of the analysis of the qualitative interview data was to assess participant experience of following the diets by identifying factors that facilitated adherence and factors that acted as barriers to adhering to the diet. It also aimed to assess whether differences exist between the intervention groups

in terms of the barriers and facilitators identified. As data were collected at two timepoints for a subset of participants (at the end of the intervention and 6 months later) the analysis was also able to explore experiences of maintaining behaviour change, to identify whether barriers and facilitators of adherence changed over time.

The following research questions were identified to address these aims:

1. What factors facilitated adherence to each diet?
2. What factors limited adherence to each diet?
3. Did experiences of adherence differ between the intervention groups?
4. Did the interventions incite maintenance of behaviour change, following trial completion?

The specific aims of this analysis tie in with the original aim of the interviews to be conducted as part of the SWiFT trial described in section4.3.10, which was to inform future research by identifying factors which may help to improve adherence to dietary restriction during chemotherapy.

5.2.4.2 Qualitative Analysis

Qualitative data analysis was assisted by Nvivo 10 software[229].

Data from the anonymised transcripts were analysed using the framework method, a form of thematic analysis[227]. This form of analysis is appropriate for these data, as it is flexible enough that it can be used for both inductive and deductive analysis[228]. This is appropriate for this study as interviews were originally conducted in a semi-structured manner, with a list of *a priori* questions that it aimed to answer, meaning initial themes of interest and theoretical constructs could be analysed in a deductive approach. At the same time, the approach is flexible enough for these *a priori* issues to be expanded and altered in an inductive manner, as the analysis progresses. This also allows any concepts of interest that may not have been identified for inclusion in the quantitative questionnaires, to be identified and explored qualitatively. Also, as the framework approach is not tied to any particular epistemological stance, it is a pragmatic choice that fits with the methodology used within this thesis[257].

The framework approach consists of a systematic series of steps or stages which take the data from individual interview transcripts, through to a matrix of data, based around rows of individual participants (cases), columns of themes and sub themes (codes) and crosscutting cells of summarised

data, which are used to aid interpretation of the data[228]. The stages used in this analysis are described in further detail below.

5.2.4.2.1 Familiarisation

Transcripts from each interview were read in full to become familiar with the interviews and the topics covered. As the interviews were not conducted by the researchers completing the analysis, the B-AHEAD 2 trial protocol and interview topic guides also aided familiarisation, giving context as to when and why the interviews were originally conducted.

5.2.4.2.2 Indexing

A coding index was developed that was based on the interview topic guide and the behavioural change concepts analysed in the quantitative analysis. Codes derived from the interview topic guide included barriers, facilitators, and motivators. Codes derived from the behavioural change concept included eating style, self-efficacy, and long-term barriers/facilitators (to capture one aspect of habit formation).

These codes were then applied to a subset of interviews initially, completed by a single researcher (ES), then reviewed by a second researcher (GH) to ensure both consistency of coding and grounding in the original data. Any inconsistencies in themes or coding were discussed and resolved between the two researchers.

5.2.4.2.3 Development of the analytical framework

The coding index developed above, was then used to sort the codes into themes. This analytical framework was then applied to the remaining interviews, though an inductive approach to analysis was also used, allowing emergent themes to alter the coding as the analysis progressed. Again, the themes were originally developed by one researcher (ES), then reviewed by and refined with a second researcher (GH).

5.2.4.2.4 Development of a framework matrix

After the analytical framework had been applied to the remaining transcripts, a framework matrix was created using participants responses to each theme. This involved summarising the data, by code, for each interview transcript. This allows the data to be compared both within individual interviews and also between participants[228]. It allowed for comparisons to be made between the intervention groups for this particular analysis.

5.2.4.2.5 Interpretation

The content of the key themes from the matrix was then summarised narratively, to aid interpretation of the results. Relationships between the themes and the intervention groups were compared for an understanding of how the experiences of the interventions differed between groups.

5.2.5 Mixed Methods Synthesis

Finally, the quantitative and qualitative data were synthesised, using a mixed methods synthesis.

The aim of the quantitative analyses was to assess the behavioural and psychological factors which motivate or reduce adherence to the diets. The aim of the qualitative analyses was to further explore participant experience of adherence, focusing on providing more in-depth data on the potential barriers to, and facilitators of, adherence that were also measured in the quantitative analysis. For this mixed methods synthesis, the quantitative and qualitative data were used in combination, using the strengths of each to allow for a more in-depth analysis of some of the issues surrounding feasibility of dietary restriction during chemotherapy[152].

There are a number of methods which can be employed to integrate quantitative and qualitative methods in a mixed methods design, depending on when the data are collected and analysed (sequential or parallel), whether precedence is given to one particular method, and at what stage of the analysis the data are integrated[258]. Within this analysis, the concurrent triangulation design was utilised. This design involves the concurrent, but separate, collection and analysis of quantitative and qualitative data in order to answer the research questions (Figure 5-1)[151].

Within the concurrent triangulation design, both methods are implemented during the same timeframe and are also afforded equal weight[151]. Affording both methods equal weight within this analysis allows the strengths of both to be utilised to provide a more in depth understanding of the factors which effect adherence to IER, and how this may differ to CER. Ultimately, the aim of providing this more in-depth knowledge, is to help to inform future interventions of energy restrictive diets during cancer treatment.

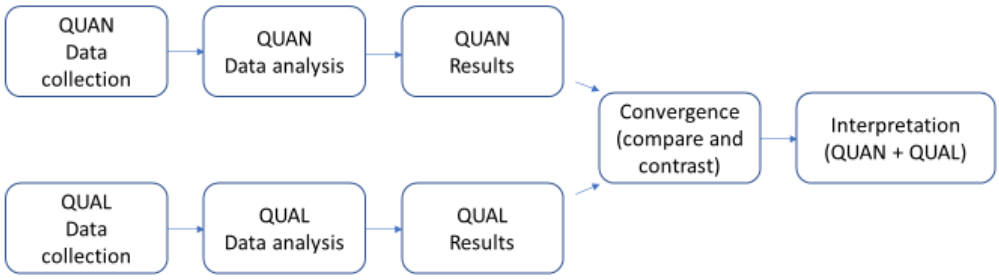

Figure 5-1 - Concurrent Triangulation Design (Convergence Mode) adapted from Creswell et al, 2006[151].

Triangulation within mixed methods research refers to the process of using different methods to gain a more complete picture of the topic being addressed by the research. It involves outlining where findings from each method converge, offering complementary information and also highlighting any discrepancies between the data[153]. The quantitative and qualitative data were analysed separately as described above, and integrated at the interpretative/reporting stage for this mixed methods analysis[155]. In this way the convergence model of triangulation was followed. Results from each component were compared and contrasted, using the data triangulation method[151, 156]. Specifically, the results were integrated through narrative, using the weaving approach, where the findings from both the qualitative and quantitative methods are drawn together narratively, in a theme by theme or concept-by concept basis[155]. Integrating the results of both the quantitative and qualitative analyses in this way allows for a more in depth interpretative narrative of the results [154].

5.3 RESULTS

5.3.1 Quantitative Results

The Consort flow diagram showing the progress of participants through the B-AHEAD 2 trial will be published with the main trial results, by the lead research team in Manchester. A summary is shown in figure 5-2, below. 172 women were randomised, though two women assigned to the IER group and one woman assigned to the CER group were found ineligible following randomisation and did not receive the intervention. This left a total of 85 women in the IER group and 84 women in the CER group.

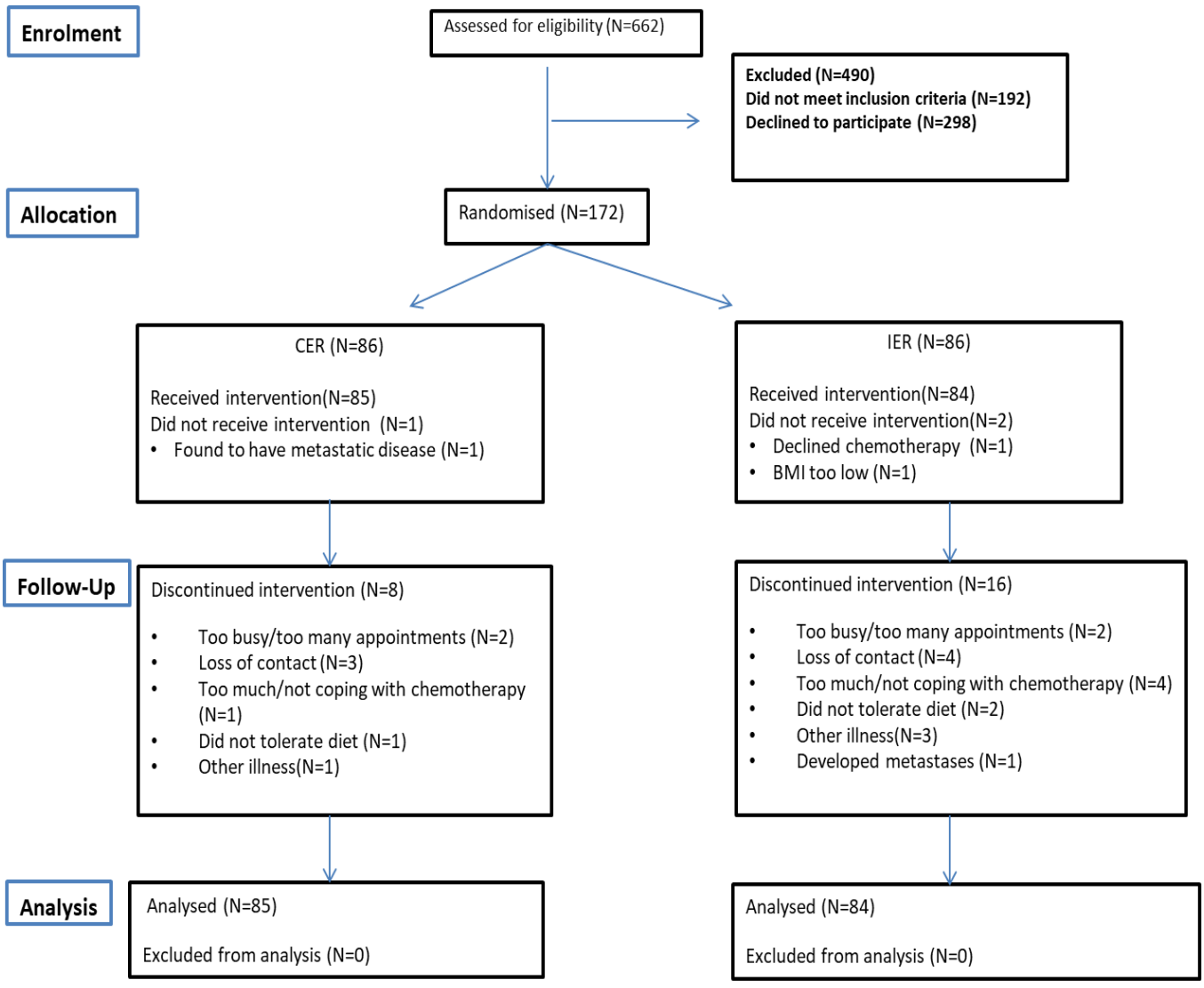

Figure 5-2 B-AHEAD 2 Consort flow diagram

*Table 5-1: **B-AHEAD 2 Trial Participant Baseline Characteristics****

Variable	Intermittent Energy Restriction (n= 84^)	Continuous Energy Restriction (n= 85^)
Age (yr) mean (SD)	51.2(9.0)	52.6(10.1)
Ethnicity:		
White	79(94.1)	78(91.8)
Black	0(0)	2(2.4)
Pakistani	3(3.6)	1(1.2)
Mixed:White & black	0(0)	3(3.5)
Chinese	0(0)	1(1.2)
Other	2(2.4)	0(0)
BMI (kg/m^2) mean (SD)	28.2(6)	28.4(6)
Menopausal status		
Pre	3(3.6)	4(4.7)
Pre/peri	44(52.4)	42(49.4)
Post	37(44)	39(45.9)
Smoking status		
Never	41(48.8)	57(67.9)
Past	37(44)	24(28.6)
Smoker	6(7)	3(3.6)
IMD		
1	15(17.9)	16(18.8)
2	13(15.5)	13(15.3)
3	14(16.7)	16(18.7)
4	23(27.4)	23(27.1)
5	19(22.6)	17(20)
Children living at home		
Yes	45(53.6)	42(49.4)
No	39(46.4)	43(50.6)
Invasive Grade 3 Tumour		
Yes	54(64.3)	44(51.8)
No	30(35.7)	41(48.2)
Chemotherapy regimen~		
DOC-C	2(2.6)	5(6.4)
EC	6(7.7)	4(5.1)
EC-DOC	3(3.9)	4(5.1)
EC-PAC	2(2.6)	4 (5.1)
FEC	1(1.3)	2(2.6)
FEC-DOC	51 (65.4)	49(62.8)
FEC-PAC	11(14.1)	10(12.8)
PAC	2(2.6)	0(0)

* Data are shown as n(%), unless otherwise stated

^ Figures show maximum number included

BMI: Body Mass Index

IMD: Index of Multiple Deprivation- quintiles based on rank

~Chemotherapy Regimen: C: Cyclophosphamide; DOC: Doxorubicin; EC: Epirubicin, Cyclophosphamide; FEC; Fluorouracil, epirubicin, cyclophosphamide; PAC: Paclitaxel;

*Table 5-2: **Comparison of baseline characteristics between those with missing and complete weight and dietary adherence data* in both intervention groups, combined***

Variable	Complete Adherence Data n= 106	Missing Adherence Data n=66	p-value^	Complete Weight Data n=143	Missing Weight Data n=29	p-value^
Age (yr) mean (SD)	53.5(10.0)	49.3(8.4)	<0.01	52.5(9.8)	48.7(8.0)	0.06
Ethnicity:						
White	99(93.4)	58(92.1)	0.50	132(92.3)	25(96.2)	0.88
Black	0(0.0)	2(3.2)		2(1.4)	0(0.0)	
Pakistani	3(2.8)	1(1.6)		3(2.1)	1(3.9)	
Mixed: White & black	2(1.9)	1(1.6)		3(2.1)	0(0.0)	
Chinese	1(0.9)	0(0.0)		1(0.7)	0(0.0)	
Other	1(0.9)	1(1.6)		2(1.4)	0(0.0)	
BMI (kg/m^2) median (IQR)	27.0(24.0, 30.0)	27.5(24.0, 32.3)	0.51	27.0 (24.0, 30.0)	28.9 (24.7, 33.5)	0.20
Menopausal status n (%):						
Pre	4(3.8)	3(4.8)	0.56	6(4.2)	1(3.9)	0.75
Pre/peri	51(48.1)	35(55.6)		71(49.7)	15(57.7)	
Post	51(48.1)	25(39.7)		66(46.2)	10(38.5)	
Smoking status:						
Never	69(65.1)	29(46.8)	<0.01	88(61.5)	10(40.0)	<0.01
Past	35(33.0)	26(41.9)		51(35.7)	10(40.0)	
Smoker	2(1.9)	7(11.3)		4(2.8)	5(20.0)	
IMD :						
1	18(17.0)	13(20.6)	0.17	27(18.9)	4(15.4)	0.42
2	14(13.2)	12(19.1)		22(15.4)	4(15.4)	
3	23(21.7)	7(11.1)		27(18.9)	3(11.5)	

4	25(23.6)	21(33.3)		35(24.5)	11(42.3)	
5	26(24.5)	10(15.9)		32(22.4)	4(15.3)	
Children living at						
home:	50(47.2)	37(58.7)	0.15	72(50.4)	15(57.7)	0.49
Yes	56(52.8)	26(41.3)		71(49.7)	11(42.3)	
No						
Invasive Grade 3						
Tumour:						
Yes	61(57.6)	37(58.7)	0.88	83(58.0)	15(57.7)	0.97
No	45(42.5)	26(41.3)		60(42.0)	11(42.3)	
Chemotherapy						
regimen:	2(3.7)	5(4.9)	0.26	7(5.3)	0(0.0)	0.18
DOC-C	6(11.1)	4(3.9)		6(4.6)	4(16.7)	
EC	1(1.9)	6(5.9)		7(5.3)	0(0.0)	
EC-DOC	1(1.9)	5(4.9)		6(4.6)	0(0.0)	
EC-PAC	2(3.7)	1(1.0)		2(1.5)	1(4.2)	
FEC	37(68.5)	63(61.8)		83(62.9)	17(70.8)	
FEC-DOC	5(9.3)	16(15.7)		19(14.4)	2(8.3)	
FEC-PAC	0(0.0)	2(2.0)		2(1.5)	0(0.0)	
PAC						

*Data are shown as n(%), unless otherwise stated

^Test statistics shown are from t-test for age, Mann-Whitney for BMI and Chi^2 for the remaining categorical variables

BMI: Body Mass Index

IQR: Interquartile Range

IMD: Index of Multiple Deprivation- quintiles based on rank

Chemotherapy Regimen: C: Cyclophosphamide; DOC: Doxorubicin; EC: Epirubicin, Cyclophosphamide; FEC; Fluorouracil, epirubicin, cyclophosphamide; PAC: Paclitaxel;

5.3.1.1 Baseline Characteristics

Baseline characteristics are shown in Table 5-1. Most participants were white, and the most common chemotherapy regimen received was FEC-docetaxel. The characteristics were broadly similar between the two intervention groups, with a slightly higher proportion of current smokers in the CER than IER group, though this observation is based on small numbers.

5.3.1.2 Missing Data

Baseline characteristics of those with complete end of trial weight and adherence data were compared to those with missing data and results are summarised in Table 5-2. Differences can be seen between the groups in terms of age and smoking status. Participants with complete adherence and weight had a higher mean age, and a higher proportion of "never" smokers.

5.3.1.3 Analysis 1: The effect of the intervention on behaviour scores.

As data in each scale were not normally distributed, a Wilcoxon test was used to compare scores from baseline and end of trial for each intervention group, to assess whether the interventions altered behaviour change scores. The results are outlined in Table 5-3.

Behavioural concept scores at baseline and end of trial were similar across the two treatment groups and change in scores were broadly similar across groups (Table 5-3). In the CER group there was some evidence for an increase in perceived behavioural control, perceived benefit and habit and automaticity. In the IER group there is evidence for an increase in perceived behavioural control. There was little change in total self-efficacy in either group. In relation to style of eating, both groups showed an increase in restrained eating and decreases in externally motivated eating. A decrease in the emotional eating style score can also be seen in the IER group.

There were no differences between treatment groups for change in any of the scores (Table 5-3).

As the results presented in Table 5-3 cluster around the same value for some scales, though the p-values indicates a difference between scores, Table 5-4 has also been provided to aid interpretation of the results. Table 5-4 reports the proportion of participants with scores at the higher end of each scale i.e., 3 or 5 (out of 5) for perceived behavioural control, perceived benefit and eating style and the proportion with a score of 5-7 (out of 7) for habit and automaticity.

Table 5-3: ***Median (IQR) behavioural concept scores at baseline and follow-up by treatment group and Mann-Whitney tests comparing scores between intervention groups at end of the trial.***

Behavioural Concept	IER			CER			Between-group end of trial comparison
	Baseline	End of Trial	Wilcoxon p-value*	Baseline	End of Trial	Wilcoxon p-value	Mann-Whitney p-value
Perceived Behavioural Control	2.2 (1.8-2.4)	3.0 (2.5-3.2)	<0.01 (n=66)	2.2 (2.0-2.4)	2.9 (2.4-3.4)	<0.01 (n=73)	0.55
Perceived Benefit	2.0 (2-3)	2.0 (1-3)	0.81 (n=65)	2.0 (2-3)	2.0 (1-2)	0.02 (n=74)	0.36
Total self-efficacy	59.0 (49.0-69.0)	61.5 (51.0-72.0)	0.10 (n=66)	61.0 (53.0-69.5)	58.0 (52.0-70.0)	0.43 (n=74)	0.45
Habit and automaticity	4.0 (2.3-6.0)	4.9 (3.5-6.0)	0.65 (n=65)	4.3 (2.6-5.5)	5.0 (3.5-6.0)	0.03 (n=71)	0.30
Eating style							
Restrained	3.1 (2.7-3.4)	3.3 (2.8-3.7)	<0.01 (n=66)	3.0 (2.6-3.7)	3.3 (3-3.8)	0.01 (n=74)	0.63
External	2.8 (2.5-3.2)	2.7 (2.3-3.0)	<0.01 (n=66)	2.8 (2.4-3.2)	2.6 (2.3-2.9)	<0.001 (n=74)	0.59
Emotional	2.5 (2.0-3.0)	2.2 (1.6-2.8)	<0.001 (n=66)	2.3 (1.9-2.8)	2.2 (1.9-2.7)	0.19 (n=74)	0.73

Perceived Behavioural Control and Benefit: score range = 1-5, higher score indicates higher perception of control/benefit
Total Self-Efficacy: score range = 14-95, higher score indicates a higher level of self-efficacy
Habit and automaticity scale: range = 1-7, higher score indicates stronger habit formation
Eating style scores taken from Dutch Eating Style Questionnaire: range = 1-5, higher score indicates eating behaviour is more restrained or cued by external or emotional factors, respectively.
* Comparing baseline and end of trial

*Table 5-4: **Proportion (%) of participants with a score of 3 and above for Perceived Behavioural Control, Perceived Benefit and Eating Style and a score of 5 and above for Habit and Automaticity.***

Behavioural Concept	IER		CER	
	Baseline	**End of Trial**	**Baseline**	**End of Trial**
Perceived Behavioural Control	6/83 (7.2)	53/66 (80.3)	4/84 (4.8)	48/74 (64.9)
Perceived Benefit	22/83 (26.5)	40/65 (61.5)	27/84 (32.1)	28/75 (37.3)
Habit and automaticity	38/82 (46.3)	51/66 (77.3)	34/80 (42.5)	54/75 (72.0)
Eating style				
Restrained	50/83 (60.2)	64/66(97.0)	48/84 (57.1)	70/75 (93.3)
External	34/83 (41.0)	39/66 (59.1)	29/84 (34.5)	26/75 (34.7)
Emotional	23/83 (27.7)	29/66 (43.9)	14/84 (16.7)	19/75 (25.3)

Perceived Behavioural Control and Benefit: score range = 1-5, higher score indicates higher perception of control/benefit
Habit and automaticity scale: range = 1-7, higher score indicates stronger habit formation
Eating style scores taken from Dutch Eating Style Questionnaire (range 1-5), higher score indicates eating behaviour is more restrained or cued by external or emotional factors, respectively.

When considering the proportion of women with a score of three or above for perceived behavioural control and perceived benefit, there appears to be a higher proportion of women in the upper half of the scales at end of trial, compared to baseline, in both intervention groups (Table 5-4). Although an overall reduction in median scores for external and emotional eating styles was previously noted, interestingly, there was an increase in the proportion of participants in the upper half of both of these scales, in the IER group and in the emotional scale in the CER group.

Regarding the habit and automaticity scale, Table 5-3 indicates there was an increase in score from baseline to end of trial, in both groups. Similarly, Table 5-4 shows that there was also an increase in the proportion of women with a score of 5 and above on this scale at the end of the trial, compared to baseline, in both groups.

5.3.1.4 Analysis 2: Comparing adherence between the intervention groups.

The average daily target energy intake was 1343 kcals (range= 1106 to 1688 kcals) and 1379 kcals (range = 1070 to 2009 kcals), in the IER and CER groups, respectively. Actual average daily energy intake reported in the end of trial 7-day diet diaries was 1389 kcals (range= 917– 2276 kcals) in the IER group and 1437 kcals (range= 773 to 2114 kcals) in the CER group.

Table 5-5 reports the number of participants classed as adherent in each intervention group. Adherence appears lower in the IER group, however, a logistic regression analysis of adherence by intervention group found that intervention group did not predict adherence (coefficient=-0.2,

SE=0.4, p = 0.59). The regression was repeated including all participants, assuming that those with missing data were not adherent and again, intervention group was not found to predict adherence (coefficient= 0.2, SE=0.3, p = 0.47).

*Table 5-5: **Number (%) of participants classed as adherent and non-adherent according to end of trial diet diaries, stratified by intervention group.***

	Intermittent Energy Restriction Group n=84	**Continuous Energy Restriction Group n=85**	**Total n=169**
Adherent	37(44.1)	43(50.6)	81(47.9)
Non-adherent	16(19.1)	23(27.1)	39(23.1)
Missing*	31(36.9)	19(22.4)	49(29.0)

*Participants were considered to have "missing" adherence data if at least one day of self-reported diet diaries were not completed.

*Table 5-6: **Weekly number (%) of participants classed as adherent and non-adherent, according to diet diaries completed across one mid-treatment cycle of chemotherapy, by intervention group.***

	Intermittent Energy Restriction Group n=84			**Continuous Energy Restriction Group n=85**		
	Week 1	**Week 2**	**Week 3**	**Week 1**	**Week 2**	**Week 3**
Adherent	33(39.3)	31(36.9)	33(39.3)	46(54.1)	42(49.4)	41(48.2)
Non-adherent	16(19.1)	16(19.1)	14(16.7)	18(21.2)	21(24.7)	21(24.7)
Missing*	35(41.7)	37(44.1)	37(44.1)	21(24.7)	22(25.9)	23(27.1)

*Participants were considered to have "missing" adherence data if at least one day of self-reported diet diaries were not completed.

Table 5-6 describes levels of adherence across one full cycle of chemotherapy. Adherence was highest in the first week of the chemotherapy cycle, though rates of self-reported adherence remained fairly consistent across the cycle in both intervention groups.

5.3.1.5 Analysis 3: Baseline behaviour scores (self-efficacy, habit formation and eating style) as predictors of adherence or weight change in each group.

Results from the regression model (Table 5-7) indicate that there was no statistical evidence for an association between adherence and baseline values of perceived behavioural control, perceived benefit, or restrained eating stye, as the confidence intervals were wide and contained the null

value. In the unadjusted model, the odds of being adherent in the CER group were 10% higher per unit change (change in one score point within the scale) in baseline total self-efficacy score, and this association remained in the adjusted model. This association can also be seen within the IER group in the adjusted model. The odds of adhering to the diet in the IER group were also higher in participants with a higher habit and automaticity score at baseline, in the unadjusted and adjusted models. Also within the IER group, external and emotional eating styles at baseline were associated with lower odds of adhering in the unadjusted models. However, the statistical evidence for the association was reduced for external eating, after adjusting for baseline age, height, weight and deprivation score, in the CER group.

*Table 5-7: **Odds ratios* and 95% Confidence Intervals from a logistic regression on the effect of baseline behavioural change scores on diet adherence.***

Behavioural Concept	Intermittent Energy Restriction						Continuous Energy Restriction					
	Unadjusted Odds Ratios			Adjusted Odds Ratios^			Unadjusted Odds Ratios			Adjusted Odds Ratios^		
	Odds Ratio	95% CI	n	Odds Ratio	95% CI	n	Odds Ratio	95% CI	n	Odds Ratio	95% CI	n
Perceived Behavioural Control	1.2	0.42, 3.19	83	1.1	0.37, 3.54	77	0.6	0.18, 2.16	84	1.0	0.26, 3.58	80
Perceived Benefit	1.3	0.74, 2.25	83	1.3	0.72, 2.43	77	0.8	0.44, 1.33	84	0.8	0.45, 1.45	80
Total self-efficacy	1.0	1.00, 1.08	83	1.1	1.01, 1.10	77	1.1	1.01, 1.10	84	1.1	1.01, 1.10	80
Habit and automaticity	1.3	1.03, 1.74	82	1.3	1.00, 1.82	76	1.0	0.77, 1.33	80	1.1	0.80, 1.45	76
Eating style												
Restrained	1.5	0.65, 3.29	83	1.2	0.50, 3.07	77	0.7	0.41, 1.26	84	0.7	0.35, 1.20	80
External	0.3	0.11, 0.87	83	0.3	0.08, 0.89	77	0.4	0.16, 1.01	84	0.4	0.17, 1.12	80
Emotional	0.3	0.16, 0.64	83	0.3	0.12, 0.63	77	0.5	0.26, 1.03	84	0.5	0.30, 1.14	80

* Odds ratios comparing the odds of being adherent to non-adherent. Results represent a one unit increase in reported behavioural concept scale score.
^Results were adjusted for baseline age, height, weight and deprivation score as potential confounders.

To explore baseline predictors of weight change, change in weight from baseline to end of trial was calculated. Participants lost an average of 2.06kgs (SD=4.3) and 0.87kgs (SD=3.60) in the IER group and CER group, respectively. None of the baseline behaviour concepts were found to predict weight change in either the IER or CER groups (Table 5-8).

When stratified into normal weight and overweight/obese groups, habit and automaticity was found to predict weight change in overweight/obese women in the CER group, only (Table 5-9).

*Table 5-8: **Regression analysis of baseline behavioural concept scores associated with weight change.***

Behavioural Concept	Intermittent Energy Restriction						Continuous Energy Restriction					
	Unadjusted			Adjusted^			Unadjusted			Adjusted^		
	Co-efficient*	p-value	n	Co-efficient*	p-value	n	Co-efficient*	p-value	n	Co-efficient*	p-value	n
Perceived Behavioural Control	-0.7	0.55	65	0.0	0.99	61	0.0	0.97	76	-0.7	0.50	73
Perceived Benefit	0.1	0.93	65	0.1	0.84	61	1.0	0.08	76	0.8	0.12	73
Total self-efficacy	0.0	0.86	65	0.0	0.32	61	0.0	0.86	76	0.0	0.70	73
Habit and automaticity	-0.2	0.52	64	-0.3	0.29	60	0.5	0.06	73	0.5	0.08	70
Eating style												
Restrained	0.0	1.00	65	-0.2	0.84	61	0.1	0.81	76	0.1	0.90	73
External	2.0	0.07	65	0.3	0.76	61	-1.0	0.22	76	-1.0	0.22	73
Emotional	1.1	0.14	65	0.4	0.53	61	-0.2	0.73	76	-0.1	0.84	73

*Values reflect average weight change(kg) per unit increase in baseline behaviour score.
^Results were adjusted for baseline age, height, weight and deprivation score as potential confounders.

*Table 5-9: **Regression analysis of baseline behavioural concept scores associated with weight change, stratified by baseline BMI category^.***

Behavioural Concept	Normal Weight Group						Overweight/Obese group					
	Intermittent Energy Restriction			Continuous Energy Restriction			Intermittent Energy Restriction			Continuous Energy Restriction		
	Co-efficient*	p-value	n	Co-efficient	p-value	n	Co-efficient	p-value	n	Co-efficient	p-value	n
Perceived Behavioural Control	2.0	0.34	14	-1.4	0.64	18	-0.5	0.74	47	-1.3	0.34	55
Perceived Benefit	1.3	0.53	14	0.7	0.58	18	0.0	0.98	47	0.8	0.19	55
Total self-efficacy	-0.1	0.19	14	0.1	0.22	18	0.0	0.92	47	0.0	0.40	55
Habit and automaticity	0.9	0.20	14	0.3	0.70	17	-0.3	0.29	46	0.7	0.03	53
Eating style												
Restrained	-1.3	0.38	14	0.5	0.68	18	0.0	0.97	47	0.2	0.74	55
External	0.9	0.64	14	0.4	0.86	18	0.2	0.91	47	-1.3	0.15	55
Emotional	0.0	0.99	14	-0.2	0.89	18	0.0	0.96	47	0.0	0.96	55

*Values reflect average weight change(kg) per unit increase in baseline behaviour score
^Results were adjusted for baseline age, height, weight and deprivation score as potential confounders.

5.3.1.6 Analysis 4: Associations of changes in behaviour scores from baseline to end of trial are with adherence or weight change in each group.

The difference in behaviour scores between baseline and end of trial was calculated.

None of the differences in behaviour scores in the IER group were associated with adherence in either the unadjusted or adjusted models, as confidence intervals were wide and contained the null value (Table 5-10). In the CER group, an increase in restrained eating style was associated with adherence in the unadjusted model, and this association remained when adjusted for age and BMI, however the confidence interval was wide (adjusted OR=5.28, 95%CI=1.54 to 18.09).

Results from the regression analysis of the association between change in behaviour scores and weight change are shown in Table 5-11. No associations were found between change in perceived behavioural control or self-efficacy and weight change.

An increase in perceived benefit was associated with an increase in weight in the IER group in both the unadjusted and adjusted models. An increase in habit and automaticity score was not associated with weight change in the IER group, although it was associated with a reduction in weight in the CER group in both models (adjusted model: 0.6kg weight loss, p=0.01)

Regarding eating style, changes in restrained and external eating styles were not found to be associated with weight change in either intervention group. Each unit increase in emotional eating style was associated with a 2.9kg weight gain in the IER group in the unadjusted model, however the statistical evidence for this was reduced in the adjusted model (co-efficient=2.2, p-value=0.06)

*Table 5-10: **Odds ratios* and 95% Confidence Intervals from a logistic regression on the effect of change in behavioural concept scores from baseline to end of trial on dietary adherence.***

Behavioural Concept	Intermittent Energy Restriction						Continuous Energy Restriction					
	Unadjusted Odds Ratios			Adjusted Odds Ratios^			Unadjusted Odds Ratios			Adjusted Odds Ratios^		
	Odds Ratio	95% CI	n	Odds Ratio	95% CI	n	Odds Ratio	95% CI	n	Odds Ratio	95% CI	n
Perceived Behavioural Control	0.9	0.44, 1.68	66	1.0	0.49, 2.20	62	1.4	0.74, 2.67	73	1.2	0.59, 2.40	70
Perceived Benefit	0.6	0.37, 1.11	65	0.7	0.37, 1.21	61	1.1	0.66, 1.89	74	1.0	0.60, 1.81	71
Total self-efficacy	1.0	0.98, 1.07	66	1.0	0.97, 1.07	62	1.0	0.98, 1.06	74	1.0	0.97, 1.06	71
Habit and automaticity	1.0	0.72, 1.40	65	1.0	0.69, 1.42	61	1.2	0.94, 1.64	71	1.2	0.87, 1.55	68
Eating style												
Restrained	0.8	0.31, 2.27	66	0.7	0.22, 2.30	62	4.7	1.50, 14.80	74	5.7	1.56, 20.55	71
External	1.4	0.48, 4.11	66	1.8	0.55, 6.23	62	2.1	0.55, 8.31	74	2.2	0.51, 9.43	71
Emotional	1.4	0.43, 4.43	66	2.4	0.63, 8.84	62	0.8	0.30, 1.89	74	0.7	0.26, 1.93	71

* Odds ratios comparing the odds of being adherent to non-adherent. Results represent a one unit increase in reported behavioural concept scale score.
^Results were adjusted for baseline age, height, weight and deprivation score as potential confounders.

*Table 5-11: **Regression analysis of change in behavioural concept scores from baseline to end of trial associated with weight change.***

Behavioural Concept	Intermittent Energy Restriction						Continuous Energy Restriction					
	Unadjusted			Adjusted^			Unadjusted			Adjusted^		
	Co-efficient*	p-value	n	Co-efficient*	p-value	n	Co-efficient*	p-value	n	Co-efficient*	p-value	n
Perceived Behavioural Control	-0.9	0.22	65	-0.7	0.32	61	-1.1	0.06	73	-0.6	0.26	70
Perceived Benefit	1.3	0.03	64	1.0	0.05	60	0.2	0.63	74	0.1	0.75	71
Total self-efficacy	-0.1	0.03	65	-0.1	0.10	61	-0.1	0.15	74	0.0	0.79	71
Habit and automaticity	-0.5	0.19	64	-0.4	0.20	60	-0.5	0.04	71	-0.6	0.01	68
Eating style												
Restrained	-1.2	0.27	65	-1.2	0.26	61	-0.7	0.28	74	-0.5	0.40	71
External	0.2	0.85	65	0.1	0.96	61	0.5	0.69	74	0.4	0.73	71
Emotional	2.9	0.03	65	2.2	0.06	61	0.4	0.63	74	-0.3	0.71	71

*Values reflect weight change(kg) per unit increase in behaviour score from baseline to end of trial
^Results were adjusted for baseline age, height, weight and deprivation score as potential confounders.

When the groups were stratified into normal and overweight/obese categories, none of the differences in behaviour change concepts in the IER group were associated with weight change in normal weight women (Table 5-12). In overweight/obese women, an increase in perceived benefit was associated with weight gain (1.2kg, p=0.05). An increase in emotional eating style was also associated with a 3.0kg increase in weight in this group (p=0.04) (Table 5-12).

Similarly, none of the differences in behaviour change scores were associated with weight change in normal weight women in the CER group. In the overweight/obese group, an increase in habit and automaticity score was associated with a weight loss of 0.8kg (p<0.01) (Table 5-12).

*Table 5-12: **Regression analysis of change in behavioural concept scores from baseline to end of trial associated with weight change, stratified by baseline BMI category^.***

Behavioural Concept	Normal Weight Group						Overweight/Obese group					
	Intermittent Energy Restriction			Continuous Energy Restriction			Intermittent Energy Restriction			Continuous Energy Restriction		
	Co-efficient*	p-value	n	Co-efficient	p-value	n	Co-efficient	p-value	n	Co-efficient	p-value	n
Perceived Behavioural Control	-0.4	0.83	14	-1.5	0.20	18	-0.9	0.31	47	-0.2	0.78	52
Perceived Benefit	1.1	0.38	13	-1.3	0.20	18	1.2	0.05	47	0.6	0.23	53
Total self-efficacy	0.0	0.81	14	0.1	0.59	18	-0.1	0.13	47	0.0	0.67	53
Habit and automaticity	-0.6	0.30	14	-0.3	0.65	17	-0.3	0.52	46	-0.8	<0.01	51
Eating style												
Restrained	-1.2	0.64	14	3.1	0.18	18	-1.1	0.39	47	-0.9	0.18	53
External	-2.3	0.17	14	-1.6	0.47	18	0.0	0.99	47	1.4	0.34	53
Emotional	0.5	0.83	14	-1.8	0.43	18	3.0	0.04	47	-0.2	0.78	53

*Values reflect weight change(kg) per unit increase in baseline behaviour score from baseline to end of trial
^Results were adjusted for baseline age, height, weight and deprivation score as potential confounders.

*Table 5-13: **Summary of change in behavioural concepts and key associations of behavioural concepts^ with adherence and weight change, stratified by intervention group.***

Behavioural Concept	Change in behavioural score from baseline to end of trial		Adherence		Weight Change	
	IER	CER	IER	CER	IER	CER
Perceived Behavioural Control	**↑***	**↑***	↑	↔	↓	↓
Total self-efficacy	↔	↔	**↑***	**↑***	↓	↔
Habit and automaticity	↑	**↑***	↑	↑	↓	**↓***
Eating style						
Restrained	**↑***	**↑***	↑	↓	↓	↓
External	**↓***	**↓***	**↓***	↓	↓	↑
Emotional	**↓***	↓	**↓***	↓	↑	↓

^ Associations with adherence are based on baseline behavioural concept scores and indicate whether the odds of adhering increased, decreased or did not change, based on a one unit increase in reported behavioural concept scale score. Associations with weight change are based on change in behavioural scores from baseline to end of trial and indicate whether weight increased, decreased or did not change based a one unit increase in reported behavioural concept scale score from baseline to end of trial.
↑ = increase/higher
↓ = reduction/lower
↔ = no change/no difference
* Indicates p<0.05 or CI did not contain 1

5.3.2 Qualitative Findings

Themes which emerged from the framework analysis are presented in four sections. First the contextual themes allow for an understanding of the context in which women joined the study and undertook the diets. Secondly the barriers to adhering to both the CER and IER groups are described and compared. Next, the facilitators of adherence to both interventions are described and compared. Finally, the experience of the longer-term adherence to the diets is described.

5.3.2.1 Participant characteristics

Semi structured interviews were conducted with a total of 13 participants; five participants from the IER group and eight from the CER group. A second interview, approximately six months after the end of the trial, was conducted with three of the IER and six of the CER group.

The sampling process described in section 5.2.1.5.2 aimed to provide a qualitative sample from both intervention groups, however Table 5-14 shows that only one participant from the normal weight category was included.

*Table 5-14: **Interview Participant Characteristics***

Participant Code	**Intervention Group** (IER/CER)	**Goal** (Weight Loss/Maintenance)	**Age**	**Follow-up interview** Yes (Y)/No (N)
1	IER	Weight Loss	43	N
2	IER	Weight Loss	49	Y
3	IER	Weight Loss	46	N
4	IER	Weight Loss	52	Y
5	IER	Weight Loss	54	Y
6	CER	Weight Loss	43	Y
7	CER	Weight Loss	57	Y
8	CER	Weight Loss	50	Y
9	CER	Weight Loss	49	Y
10	CER	Weight Loss	50	Y
11	CER	Weight Loss	49	Y
12	CER	Maintenance	48	N
13	CER	Weight Loss	49	N

5.3.2.2 Context

Contextual themes facilitated an understanding of the participants' overall experiences of undergoing chemotherapy treatment, their individual eating styles and their motivations for deciding to take part in the B-AHEAD 2 trial. These themes provide an understanding of the setting, both physical and emotional, in which the women were undertaking their new diets.

5.3.2.2.1 Experience of chemotherapy

Women started the diet following surgery, immediately prior to starting their chemotherapy treatment. This treatment journey was difficult for all the women interviewed and led to them suffering from a wide variety of chemotherapy induced toxicities including sickness, diarrhoea, constipation, neutropenia, peripheral neuropathy, oral thrush and skin rashes.

> *"When I was on the chemo you could have dropped a bomb next to me I wouldn't have cared some days… I was absolutely exhausted." (12, CER)*

> *"You lose so much when you go through chemo, your hair… you lost your dignity in places because you have your rough times and things like you've not got the same bladder control or bowel control. There's so much that people just think, oh, just take the medicine, it's not just the medicine it's all everything else that comes with it." (11, CER)*

As well as having an impact on their physical health, their mental wellbeing was also affected by the diagnosis and subsequent treatment.

> *"And then, say, one day a month I'd be crying all day and feeling proper sorry for myself and saying, I can't do this anymore, I've had enough, because I hurt that much." (6, CER)*

> *"The first three weeks after diagnosis were possibly the worst three weeks of my life. I've never been so emotionally up and down." (2, IER)*

Here, we are given an understanding of the impact of the treatment that women were dealing with when trying to embark on their new dietary regimes. As discussed in more detail below, some aspects of the treatment side effects were seen as barriers to following the prescribed diets.

5.3.2.2.2 Eating style

Emotional eating was the single eating style identified in the interviews. Many of the women were able to identify that they exhibited this style of eating, and also recognised how and when this was not conducive to following either of the diets.

> *"I am prone to, if I'm being down, comfort eating, and not just little bits, I can…I binge, I binge eat..." (1, IER)*

> *"And I'm a bit of a comfort eater as well, you know…" (10, CER)*

They acknowledged that this eating style could be exacerbated by aspects of their treatment, such as the need to comfort eat, when not feeling well, or suffering from tiredness related to treatment. Some also identified that being off work and at home could lead to boredom which in turn could lead to eating and breaking the diets:

> *"I've not spoke to anybody that hasn't comfort ate during chemo. Because you're used to going out to work or cleaning or whatever, looking after your family, you're used to being fired up on four cylinders. And then all of a sudden, you're sat and you're thinking, it's dinnertime, I'll have some dinner." (11, CER)*

> *"Because, that's my way of coping…You know, to eat something nice…To make me feel better." (3, IER)*

5.3.2.2.3 Motivation for taking part in the trial

Weight loss, or preventing treatment induced weight gain, was a common motivator for enrolling in the trial and starting the diets. Losing weight was seen to lead to an overall healthier lifestyle which would make women feel and look better. There was also some acknowledgement that weight loss may in turn reduce the risk of other lifestyle associated illnesses e.g., heart disease, diabetes and arthritis.

> *"I just want to try and just get healthy again and just lose some weight" (3, IER)*

> *"You know, because people are prone to putting weight on and it's to try and avoid it, and I was just…I could only see that it could benefit me further…" (12, CER)*

> *"The Mediterranean Diet is promoted in helping with, you know, general health, prevention of lifestyle-related diseases. So that's why. You know, and obviously I don't want to gain any more weight because I'm diabetic." (5, IER)*

Women also felt that embarking on a diet during their treatment would help to give them something to focus on, other than the treatment and feeling unwell. Some expressed that they were worried how they would fill their time while off work, so trying to follow the diet may keep them motivated and distracted.

> *"So it just seemed a way… more of a coping mechanism to get through what I had to get through" (2, IER)*

> *"It would give you something to think about other than going through chemotherapy." (3, IER)*

> *"I needed the concentration of thinking about something else that wasn't about the cancer." (6, CER)*

There was also a sense of altruism for many of the women, that taking part in research could be of benefit not just to themselves, but to other women in the future.

> *"Well, to me, a medical study helps other people, so it doesn't cost me anything to be part of it, so why not?" (4, IER)*

Finally, another common reason for taking part was the benefit of having additional contact with the hospital, the idea that they would be monitored throughout.

> *"Because they were going to check me out, physically, and I thought that could only be a good thing." (5, IER)*

A distinct difference in motivating factors for longer term dietary change could be seen in the follow-up interviews. Here the main motivator for continuing with the diet past the end of the trial, was the hope that an improved diet would reduce the chances of cancer recurrence.

> *"There is the nagging thing of the fact that if you're overweight, you could possibly get cancer again." (2, IER)*

> *"I says this diet isn't just about how I look it's about hopefully that eating healthily my cancer won't come back as well." (8, CER)*

5.3.2.3 Barriers to dietary adherence during chemotherapy

This theme identifies the barriers to following the diets during chemotherapy treatment. Overall, four barriers were found: diet preferences, treatment side effects, social influences and low self-efficacy. Two of these, dietary preferences and treatment side effects, were common across both intervention groups. The remaining two barriers, social influences and low self-efficacy, were found to be unique to the IER group.

5.3.2.3.1 Diet preferences

Women in both intervention groups found that their natural food preferences were sometimes not conducive to their prescribed diet. Examples of how their personal dietary preferences were not conducive to the diet were varied. Some found it difficult to restrict the amount of fruit and carbohydrates that they ate, while conversely some found it difficult to meet the required number of carbohydrate and dairy portions each day.

> *"I found the restrictions on the fruit a bit…a bit more. I like to get up and have a fruit salad…" (1, IER)*

> *"And I think that is the thing, it is so limited as to what you...especially if like me you don't really like fish." (2, IER)*

> *"The only thing that really for me was the carbohydrates, I found it really, really hard, started stressing about them… Because there was too many to eat in a day" (6, CER)*

> *"Apart from in tea I don't drink milk on its own… …it was still hard doing three dairy a day sometimes." (10, CER)*

> *"The thing I found hard about the Mediterranean one is sticking to it. I've obviously realised I'm quite a carb eating person. (10, CER)*

In some cases, this translated into women saying they would rather have been randomised into the other trial arm:

> *"Because there was too many to eat in a day, because I didn't…I only had kind of high protein and lowish carb before in my normal diet, so I was really hoping for the low carb diet, and I didn't get it, obviously." (6, CER)*

For two individuals, this ultimately led them to switch diets during the trial:

"Well, when I was faced with a carb free weekend it was difficult then to just eat eggs all the time…so I went on the Mediterranean diet Monday to Sunday, so that I found was fine… Much better, because that's the diet I'm on anyway." (5, IER)

"Because the science behind the 5:2 Diet and the 500 calories, it works for me, because you can't possibly make up all the calories that you've…so mentally, I was more keyed into doing that, so I ended up doing a bit of both... if I didn't drop them calories, it just didn't work. If I stuck to a 1,000 calories a day, I'd still put weight on." (11, CER)

5.3.2.3.2 Treatment side effects

Chemotherapy induced side effects were a commonly reported barrier in both intervention groups. Changes in food perception was the most frequently reported side effect to act as a barrier to following the diets, particularly in the CER group.

"So I think the whole thinking about the food because you're not interested anyway to actually do it is really, really hard work." (2, IER)

"One of the things I liked and I didn't…I thought I can't have a lot of this, was, you know orange Lucozade?" (9, CER)

"I suppose I craved…I mean, both times after chemo, especially on the day of chemo, I'd crave things like crisps…more the saltiness, I suppose….because by then, I suppose, my sense of taste was more dull." (10, CER)

"The diet's very difficult because your taste buds change…your taste buds completely go through the wall, and you're craving different things." (11, CER)

So, it's just like being…you know, sort of that pregnancy when you go off your food, some things. I went off tea when I was pregnant, went off a few other foods when I was pregnant. You yearn for certain things, like fish fingers…and done exactly the same this time." (12, CER)

Although not discussed as frequently, fatigue due to chemotherapy was also seen as a barrier to following both diets.

"But because I was so tired and couldn't get out of bed that…well you don't…the two restricted days, it was things like you need eggs for break…you need your protein and I

couldn't be bothered getting up cooking… Because especially the further you get in [to treatment] *the more tired you get, the less time you want to spend cooking" (1, IER)*

"But I think as time went on I didn't…I couldn't be bothered to make salad or…just didn't have that the mental, physical…"(7, CER)

"By Session 3, the first week of my chemo, I just gave up on even trying to use the diet. I didn't have the energy sort of after…when I was feeling well enough to be up and about I didn't have the energy to be planning what meals we were going to have the following week." (12, CER)

5.3.2.3.3 Social influences

One barrier that was identified as being unique to the IER group, was that of social influences. Some participants in this group found that, often well-meaning partners or family members, encouraged or provided food that was not conducive to the diet:

"Because my husband can't cook. He can't even handle a vegetable let alone face cooking one or eating one…So, he feels guilty that he can't cook for me. So, his idea of looking after me is getting me a takeout to save me cooking, so that doesn't help." (1, IER)

"But then she's trying to get me to have one, and I mean, I love cakes, I love cream cakes and everything, but I can say no, but a lot of the time, I don't." (4, IER)

In one example, the difficulties of fitting the IER diet into regular family eating patterns was also expressed:

"Because we're trying to eat, eat in the family, keep it together sort of thing so that was the other thing that I was perhaps sometimes cooking something completely different for me that I'm cooking for them or having to adapt things. So that made the whole eating process even harder than it already was and the cooking and all that kind of thing." (2, IER)

5.3.2.3.4 Low self-efficacy

A second barrier that was only discussed within the IER group interviews, was the concept of low self-efficacy. Women in this group, expressed doubt in their own ability to adhere to the diet, questioning their will power or ability to restrict themselves:

> *"You do need willpower and I'm not very good at that." (1, IER)*

> *"It is really hard when you've gone through some things and you try your best, and you'll be good all day and then one little thing will trigger you and you'll pig out and then you're so angry at yourself. And then it's all too easy to think oh I've messed up now I might as well just mess...not care about the rest of the day." (1, IER)*

> *"I was just not in the right frame of mind at all. I just thought, oh no, if I have that, if I do that, then I can't have that, so… I kept trying, and trying, and then I thought, no, there's no point because I can't do it." (4, IER)*

5.3.2.4 Facilitators to dietary adherence during chemotherapy

This theme identifies the facilitators of adherence to the diets during chemotherapy treatment. Two facilitators of the diets were found: dietitian support and social support. Support from the dietitian was a common facilitator across both intervention groups, while the positive impact of social support was discussed in the CER group, in particular.

5.3.2.4.1 Regular contact with the dietitian

As part of the interventions, participants were provided with a regular two-weekly consultation with the dietitian. This dietitian contact was the most commonly discussed facilitator of adherence to both diets.

> *"They always had positive...but it was positive feedback, it was positive responses and helpful suggestions." (2, IER)*

> *"It was helpful, no it was helpful, because [dietitian] was really supportive, you know, even when I said well, no, I've had toast or I've had a mince pie, she was really supportive and I think, right, I've got to try and focus back on it." (3, IER)*

"Wonderful people, very supportive, and when I was distressed they were marvelously supportive. But they're very strict when it comes to diet and exercise advice. Let me tell you." (5, IER)

"It's like you get a bit of a rapport with people, don't you, because, you know, I suppose … and you trust them that bit more, it's a natural thing, isn't it?" (9, CER)

"I'm better when you know someone else is sort of...monitoring me." (10, CER)

The contact was viewed as being supportive, not just in terms of the diet and the trial, but their overall treatment experience:

"So, that phone call once a fortnight, although it was for your research, I felt it was actually very supportive role and I found that really useful." (12, CER)

While the dietitian contact was found to be supportive and helpful, some examples were given where women felt additional time spent with the dietitian, tailoring the diet to their tastes or circumstances, would have been of further benefit to them:

"So if there had been a bit more...a couple of weeks planner with different suggestions on, that might have helped because I really was confused at first…that would be fantastic because even if you then only had two weeks and you hadn't had time to work out other things you could repeat that two weeks until you are into the swing of things." (1, IER)

"You have got ideas in the books but if it's full of things that you don't really like… it's the benefit of time to sort of devise…because I'm sure somebody could pull a programme together quite easily, couldn't they, to say, well, you could stick that one in there, and make their own menu for the sort of…" (2, IER)

"Maybe a refocus in at least some of the phone calls where…where you could then talk about better planning, and maybe draw up meal plans" (7, CER)

This suggestion was raised in interviews as a counterbalance to the difficulty that women experienced in adapting diets to their own food preferences or aversions.

5.3.2.4.2 Social support

As discussed previously, social influences were found to act as a barrier to adherence in the IER group. Conversely, social support was identified as a facilitator of adherence in the CER group. Some women found their husbands or other family members were helpful, acting as facilitators by encouraging them or preparing food for them during their treatment:

> *"Even when I was on the chemo my husband was very good at, right, you've got to eat something…" (12, CER)*

> *"My sister came up for… a couple of the chemo sessions…she can cook so… stuff out of the book" (10, CER)*

5.3.2.5 Experiences of following the diets in the longer-term

This theme explores the experiences of maintaining adherence to the diets past the end of the trial. Nine of the participants were interviewed approximately six months after their participation in the dietary interventions, six from the CER group and three from the IER group. This section provides a summary of how many of these participants reported continued adherence to the diets, and explores whether the barriers to longer-term maintenance of the diets differed from those identified during treatment.

5.3.2.5.1 Longer-term adherence to the diets

Of the six CER participants interviewed, three had continued with at least some aspects of the diet, longer term. Two had not continued with the diet but wanted to start it again in the future and one had switched from the CER diet to the IER diet following the end of trial.

Three of the women in the IER group were interviewed again approximately six months following their participation in the trial. At this time, one had continued with the IER diet, one had discontinued with the diet and one had switched to the Mediterranean diet.

5.3.2.5.2 Longer-term barriers

Three barriers to longer-term adherence were identified. Two were similar to those previously experienced: diet preferences and treatment side effects. While the additional barrier of changes in routine was also identified.

5.3.2.5.2.1 Diet preferences

Diet preferences, particularly for higher carbohydrate intake, were raised again as a barrier to following the IER diet in the long term. This was listed as the reason for not continuing with the diet in one example:

> *"Because I like carbs, I like rice, and I like pasta, and I like potatoes." (3, IER)*

It was suggested that advising how the diet could be altered to suit individual preferences in the longer-term could help improve dietary maintenance:

> *"Sometimes I'll go, oh, I'll have a vegetarian thing but I struggled with a bit of what you can actually eat vegetarian-wise as well." (2, IER)*

The participant who had switched to the Mediterranean diet, because of a personal preference for that diet, had continued to follow that diet:

> *"It suits me the best… I would, I find it [the IER diet] really hard with proteins. I find it…I'm almost a vegetarian and I do tend to eat small amounts of protein and more carbs and veg and dairy. So having a carb-free diet was too complicated." (5, IER)*

5.3.2.5.2.2 Ongoing treatment side effects

Treatment side effects remained a barrier to adherence in the longer term, in the CER group in particular. While changes in food perception had resolved, fatigue from the cancer treatment was still present for some women in this group, so they were having to navigate this while trying to maintain their diets.

> *"Because this has been a period of recovery and obviously one watches…I suppose one has got to notice more closely because there has been periods of fatigue. And it's an ongoing process and it's a development" (7, CER)*

> *"So that's a mental battle but I haven't physically got the strength to do anything about it so what do you do, where do you go?" (11, CER)*

5.3.2.5.2.3 Changes to daily routines

As women started to get back to their pre-treatment routines, with work and holidays, changes to their usual daily routine were identified as barriers to longer term diet changes, in both groups.

"We went to see my sister, and we came down on the … so we went out for a meal and I had a burger and chips. It was gorgeous. I thought, this is so naughty." (2, IER)

"Yeah, but I think the trouble is when I get started I can't have any interruptions, I can't have anything going on, do you know what I mean, I've got to be able to just think about me for a few weeks?" (11, CER)

"But then, January, I had Christmas, and I enjoyed Christmas, 'cause I thought, I don't want to be thinking about my diet at Christmas." (13, CER)

When I'm at work, in a way it's easier to be consistent because you've got a pattern, it's when you start working sometimes, and the worst time is on holiday." (7, CER)

5.4 DISCUSSION

As detailed in section 5.2.5, quantitative and qualitative findings were synthesised through narrative in this discussion section, using a weaving technique, allowing the results from both methods to be interpreted together. This section outlines how the results complement each other, converge and diverge. Results are interpreted in accordance with each other to make recommendations for future research into energy restriction interventions during chemotherapy.

5.4.1 Assessment of behaviour change

Similar to the methods used in the SWiFT feasibility trial, B-AHEAD 2 did not base their dietary restriction intervention in a named behavioural change theory, but instead aimed to identify which facilitators and barriers were of importance to the intervention by targeting and measuring three behaviour change concepts. Using this method allows for the key concepts of interest to be identified and can move towards informing which theory may be particularly applicable to future dietary restriction interventions during cancer treatment.

The B-AHEAD 2 trial targeted and measured three behaviour change concepts, to alter participants' diet: self-efficacy, habit formation and eating style. The quantitative data in this analysis was used to assess the impact of the intervention on key behaviour change measures and the associations between these concepts and adherence and weight change. The qualitative data allowed a more in-depth view into

participants experiences of altering their behaviour to follow the diets. The results are interpreted together and outlined for each concept below.

5.4.1.1 Self-efficacy

Although the B-AHEAD 2 intervention targeted dietary self-efficacy, no change in total self-efficacy score from baseline to end of trial was seen in either intervention group in the quantitative analysis. As discussed by the developers of the measurement scale, one reason for this may be that certain populations, for example those who are overweight or obese, require more intense intervention for some components of self-efficacy, than others, in order to alter self-efficacy[252]. Women recruited to this trial were undergoing chemotherapy which has negative effects on both physical and mental wellbeing[259], and so may be subject to reduced self-efficacy across various aspects of their self-care. Though little data exists in relation to diet self-efficacy in particular, previous research has identified that self-efficacy in relation to general self-care and symptom management is low in people with cancer[260]. Self-esteem, which correlates strongly with self-efficacy, has also been found to be reduced in women undergoing chemotherapy for breast cancer treatment[78, 261, 262]. It is possible that in this population the self-efficacy intervention helped participants to maintain a sense of self-efficacy, at a time when it might otherwise be reduced. The lack of a control group within this trial, however, makes these results difficult to interpret. Further research is required to identify the impact of chemotherapy on dietary self-efficacy in the absence of intervention. Understanding how chemotherapy impacts on dietary self-efficacy would allow for an assessment as to whether the impact of self-efficacy was attenuated in this group, or whether the intervention was unsuccessful at altering this potentially modifiable behaviour concept.

Within the qualitative analysis, low self-efficacy was referred to more commonly in the IER group than the CER group. Potential reasons for this could be the fact that the IER diet was deemed further away from what is considered a normal diet. Therefore, increased self-efficacy was perceived as being more important in order to be able to adhere to the diet. It may also have seemed more apparent when participants were not able to adhere to the diet, as the IER diet presented a more structured diet with clear rules, than the continuous restriction diet. However quantitative analysis found no difference in this measure between the groups at the end of the trial. Reasons for this apparent discrepancy may be due to the fact that the qualitative sample only contained one person in the weight maintenance group, so the qualitative results could reflect the barriers experienced more by people with a lower inherent diet self-efficacy, i.e., those who are overweight/obese. Alternatively, as the qualitative data are looking

at this concept from an experiential point of view, it may be capturing aspects of self-efficacy not measured within the quantitative scales used.

Previous research into self-efficacy and diet, has found that self-efficacy predicts dietary behaviour change[263]. In congruence with this, the total self-efficacy score was found to predict self-reported adherence to the diet in both intervention groups in this analysis. So, further research into how to increase the impact of interventions on dietary self-efficacy in this population is important.

One aspect of self-efficacy that was found to be increased in both intervention groups was perceived behavioural control. However, an increase in perceived behavioural control was not found to be associated with adherence or weight loss in either intervention groups. These findings suggest that the intervention was successful at altering the concept though it did not result in a corresponding weight loss. However, these results should be interpreted with caution due to the lack of a control comparison and multiple testing.

In summary, these results suggest that self-efficacy was a predictor of adherence to the dietary interventions. Women in the IER group, in particular, described low dietary self-efficacy during follow-up interviews. Taken together, this makes self-efficacy a potentially important concept for further interventions to target, to maximise adherence. Further research into how chemotherapy impacts dietary self-efficacy would increase our understanding of how this factor could be utilised to incite dietary change in future interventions that are implemented at the time of chemotherapy.

5.4.1.2 Habit formation and behaviour change maintenance

The analysis found evidence for an increase in habit and automaticity in the CER group, while an increase in this score was also associated with weight loss in the overweight/obese category in this group. This indicates that the intervention was successful at habitualising the CER diet and that these changes were associated with the desired weight loss in overweight/obese women. These results confirm the findings from previous research into the use of habit formation for weight loss in overweight individuals, outside of the chemotherapy setting[243]. One systematic review found that interventions based on habit formation theory resulted in higher weight loss compared to interventions which did not aim to induce habit formation (difference of 1.4 kg, 95% CI=0.5, 2.3, P = 0.004).

While the odds of adhering to the diet in the IER group were higher in participants with a higher habit and automaticity score at baseline, there was no evidence for an increase in this score from baseline to end of trial. Reasons for this are unclear, as it was anticipated that the higher level of restriction in this

diet would lead to habit formation in this group and there is evidence that there was an increase in the proportion of participants scoring in the upper half of this scale at end of trial. One reason for the lack of evidence for an increase in this score from baseline to end of trial may be that the sample size was not large enough to provide evidence for a change in this score from baseline to end of trial.

As discussed previously, in section 5.2.1.4.2, this measure can be used to assess the success of an intervention, where habit formation is understood to predict eating behaviour and contribute to maintenance of behaviour change[243, 247]. The addition of the qualitative data allows for an understanding of the experience of trying to maintain the diet in the longer-term, past the end of the intervention. Taking part in the trial appeared to increase women's understanding of the relationship between breast cancer and diet. A shift can be seen in the factors that motivated them to take part initially (weight loss/maintenance and offering something external to focus on during treatment), to the motivation to maintain their diet (to reduce the chances of the cancer recurring or spreading). However, a key barrier to long term change was the ongoing fatigue experienced by the women, even six months after the end of their treatment. This highlights how important support and advice is when women complete their chemotherapy treatment, to help them continue with their diets. Advice and help on how best to manage fatigue, particularly in the context of returning to usual work and lifestyle patterns, could aid adherence to the diets in the longer term.

5.4.1.3 Eating style

Eating style was altered during the intervention, with a move to a more restrained and less emotional eating style in both groups. This indicates that the techniques employed in the interventions were successful at altering eating styles to the types which are associated with less disordered eating[253]. There was less evidence for an effect of the intervention on externally cued eating. In the IER group, analysis of the eating style scores also found that the odds of adhering were higher in people with a lower baseline emotional eating style and that an increase in emotional eating score was associated with an increase in weight.

This fits with previous research into these measures which has suggested that both dietary restraint and emotional eating moderate the relationship between overconsumption and being overweight, but that an external eating style does not. It was concluded that body weight may be determined more by people's tendency toward emotional eating than by sensitivity to environmental food cues[264]. As can be seen in the qualitative analysis, chemotherapy treatment was identified as an extremely difficult time for women participating in the trial, with implications for both their physical and mental wellbeing. This

may create an environment which can lead to an increase in emotional eating, as women use eating to try to regulate the additional emotion burdens created by chemotherapy treatment. There was an acknowledgement from some women, during the interviews, that they had an inherent emotional eating style, regardless of their treatment and that this could be exacerbated by the treatment.

In combination, these results, when interpreted in the context of previous research into eating styles, identify emotional eating as a key intervention target for dietary restriction interventions implemented during chemotherapy. Providing women with information on how to cope with treatment side effects, without the use of food to regulate emotion, may help to limit weight gain during chemotherapy.

5.4.2 Assessment of adherence to energy restricted diets during chemotherapy

When compared outside of a chemotherapy setting, intermittent energy restriction has been found to have a comparable effect on weight loss and improvements in metabolic health as continuous energy restriction[265, 266]. The majority of studies have also reported similar adherence between IER and CER[265]. However, introducing energy restrictive diets within the setting of chemotherapy treatment raises the potential for issues associated with side effects and reduced quality of life, not experienced in other settings. Therefore, assessing the feasibility of introducing them within this patient group is important for informing future research.

Overall adherence (47.9%) was lower than in previously reported trials comparing IER to CER which has found adherence to range from 64% to 93%[265]. There are a number of potential reasons for this. Firstly, no standard definition for adherence has been used across trials comparing these diets, therefore differences may reflect differences in how adherence is measured and reported. Secondly, within this analysis, missing data was assumed as non-adherent, and due to the need for all 7 days of dietary data to be completed to assess adherence, the level of missing data was high. There is therefore the possibility that levels of non-adherence were overestimated, by including missing data in this way. Finally, it is also possible that adherence was lower in this trial due to the setting in which the diets were being followed. As previously discussed, the impact of chemotherapy, and the effect it has on emotional and physical wellbeing, may have made it more difficult for women to follow the interventions, than it would have been outside of this setting.

As with the findings of previous reviews of IER and CER diets, self-reported adherence did not differ between the intervention groups in this analysis. When identifying and comparing barriers to dietary adherence in the qualitative analysis, it is apparent that many of the barriers are the same across both

intervention groups (treatment side effects, dietary preferences). The exception to this was the impact of social influences. Taken together, this has implications on the assessment of the feasibility of introducing an intermittent diet during chemotherapy, as it indicates it is at least as feasible to implement, in terms of participants being able to adhere to the diet, as a more traditional continuous restriction diet. Moreover, understanding the factors which facilitated or acted as barriers to adherence, will allow for future interventions to take these factors into account, with the aim of improving adherence in future trials.

5.4.2.1 Barriers to dietary adherence

5.4.2.1.1 Treatment side-effects

Qualitative analysis identified changes in perception of food (taste and sensory changes) and fatigue caused by chemotherapy as barriers to adherence for both diets. It is understood that treatment side effects fluctuate across the chemotherapy cycle. In relationship to diet and appetite in particular, taste and appetite have been found to be reduced early in each chemotherapy cycle, but to recover later in each cycle[219]. Within the quantitative analysis, however, adherence was found to be consistent across one cycle of chemotherapy, in both intervention groups. This is of interest when studying the diets in the context of treatment, as one potential barrier to adherence could be adverse events associated with treatment. However, as self-report adherence was consistent within this analysis, this suggests that fluctuations in side effects did not affect participants ability to adhere to the diet in this trial.

As described in section 5.2.1.4, the dietary intervention delivered in B-AHEAD 2 aimed to provide women with strategies to maintain their diets, even when experiencing chemotherapy side effects. The interview data showed that changes in food perception and fatigue were the main side effects to chemotherapy treatment that made adherence to the diets challenging. The quantitative results indicate that adherence was maintained across the chemotherapy cycle, suggesting the intervention may have been successful at mitigating the impact of fluctuations of these side effects on adherence. However, this analysis only included overall energy intake, so differences may exist in quality of diet at this time.

5.4.2.1.2 Dietary preferences

Diet preferences played an important role in determining participant experiences of the diets within the qualitative analysis. They were cited as a barrier to adherence in both intervention groups. Although examples of specific preferences were varied, and even conflicting in some instances (e.g., one

participant found the carbohydrate intake too high in the CER diet while another found it too low) this highlights the level of individuality around dietary preferences. This knowledge and the fact that many of the women suggested greater tailoring of the diets to fit with their preferences or circumstances (e.g., family meals), means that this could be an important aspect to consider when aiming to improve adherence in future trials of energy restriction during cancer treatment. Within the literature, this recommendation to match diet composition to individual preferences has also been made following a growing number of dietary intervention trials[267-269].

Some participants expressed preferences over which diet they would have liked to receive. The fact that some participants switched their diet either during the trial, or at the end of the trial, also raises a question about whether a traditional RCT design is the most appropriate way to compare diets during cancer treatment. The RCT is viewed as the gold standard for clinical trial design because it is a robust design for testing the efficacy of an intervention[270]. However, poor adherence is a threat to the validity of results in this design[271, 272]. Alternative designs may be more suitable for some research questions, for example, if trial designs can reduce or limit the impact of low adherence, they can increase the generalisability of the results[272]. This can particularly be the case for trials where participants assume an active or demanding role in undertaking the intervention and when they may be likely to have strong preferences for one intervention over another[273]. This could be argued to be the case in some dietary research, where personal, cultural or social preferences play a part in shaping dietary preferences. If a participant is randomised to a treatment they do not want, they may have lower motivation to follow the intervention, resulting in poorer adherence and biased estimates of effectiveness[273]. Instead of randomising participants regardless of pre-existing preferences, working with these preferences in a more pragmatic approach could lead to increased adherence and ultimately increased external validity of the results by capitalizing on these preferences.

Alternative designs that have been suggested to combat these issues include the patient preference design[274]. This involves ascertaining participant preferences prior to randomisation, then randomly allocating patients who have no preference to either intervention 1 or 2 (groups A and B). Two further groups are then included, those who chose intervention 1 (group C) and those who chose intervention 2 (group D). Results from this form of design would give an estimate of the effectiveness of the interventions as well as the influence of preferences for the interventions[273]. However, limitations of this design include the potential for large numbers of patients to express a preference, meaning there is an insufficient number of participants willing to be randomised[275]. This design also increases the

overall number of patients required, which may lead to increase in the time and cost required to conduct the trial. As the observations regarding diet preferences within this analysis are based on a small sample size, formative research into potential participant preferences may be of use, either through a standalone observational study, or by requesting participant preferences prior to subsequent RCTs in this field.

Rather than using alternative designs to account for personal preferences, another approach could be to use qualitative intervention to challenge these presumed preferences. During the development of the QRI, described in section 4.7.1, researchers identified that although potential participant preferences were often perceived as a barrier to recruitment, they could be used to enhance informed consent and improve randomisation rates[136]. Once patient treatment preferences were identified as a potential obstacle, interventions for researchers could be developed to inform researchers how to approach treatment preferences with potential participants. For example, one literature review of studies with qualitative research methods that focused on the recruitment activity of clinicians found that while sometimes unwilling to explore or challenge participant preferences, once recruiters provided detailed discussion of interventions and their rationale with participants, their stated preferences were frequently changed[138]. The authors did, however, note that several studies also highlighted that recruiters can feel uncomfortable with being tasked with exploring and challenging participant preferences. This suggests that, while there is the potential to improve adherence by challenging participant preferences, recruiters may require training in order to empower them to challenge participants dietary preferences as part of the recruitment process.

5.4.2.1.3 Social influences

The qualitative analysis highlights the complex nature of the impact of social influences on diet, in relation to the role family members and partners play in food provision during cancer treatment. While it can be seen to act as a facilitator to following the diet in the CER group, social influences, such as partners or family members providing food, were also cited as a barrier to following the diet in the IER group. One reason for this apparent inconsistency, may be how the diets are perceived, with the IER being thought of as more “restrictive”. This can be seen in women’s descriptions of the diet itself. There is also a colloquial knowledge around cancer treatment, that people should not restrict their dietary intake, in order to try and maintain nutrition throughout their treatment[78]. This is at odds with the IER diet, where energy intake is greatly reduced, albeit for a short period of time. This may be harder to come to terms with for those who take a role in food provision for the participants, and as discussed in

section 5.4.4, highlights the potential need for inclusion of family members in future intervention delivery.

5.4.2.2 Facilitators to dietary adherence

5.4.2.2.1 Support from the dietitian

The importance of the role of the dietitian as a facilitator of the intervention was highlighted in both groups within the qualitative analysis and may be one of the reasons for the successful alterations in behaviour change concepts found in the quantitative analysis. This effectiveness of the technique of implementing a supervised dietary intervention, with regular contact is confirmed in the literature where one meta-analysis found that interventions that include supervised monitoring, compared to self-monitoring alone improves adherence rates by up to 65%[276]. While, within diabetes research, interventions provided by a dietitian compared to other health professional, lead to greater weight loss results[277]. Similarly, dietary interventions which include frequent contact have been found to maximise the intervention effect[278].

As the dietitian contact and support were so highly prized in both trial arms, it confirms that these health professionals are ideally placed for working with participants on a more individualised basis, providing them with further knowledge or tools on how to adapt their diet, where required, while still conforming to the required parameters of the diet.

5.4.2.2.2 Social Support

Within the CER group, social support, often from women's partners, can be seen to act as a facilitator to following the diet. This was through support and encouragement or provision of appropriate food. Previous research has found that weight loss interventions which include some aspect of social support, have higher adherence rates and that participants are more likely to maintain weight loss when they attend an intervention with a family member or with friends[276].

As the B-AHEAD 2 intervention did not specifically include family members within the design, and lack of social support was identified as a barrier in the IER group, further building on the concept of including social support to facilitate adherence to the intervention, could be a useful strategy in future trials.

5.4.3 Strengths and limitations

This analysis used data from one of the few trials to date to have tested dietary restriction interventions for weight loss/maintenance during chemotherapy, and the only trial to compare intermittent and

continuous restriction at this time. This provided a unique opportunity to further understand the process of behaviour change in these interventions, and the effect of these behaviour change concepts on adherence and weight change.

As a mixed method synthesis, this study was also able to draw on the strengths of both quantitative and qualitative data to further understand the feasibility of implementing dietary restriction interventions during chemotherapy for breast cancer, in terms of adherence and behaviour change. It utilised quantitative behavioural change data to understand the impact of the intervention on these measures and how they associated with adherence and weight change. The qualitative analysis looked in further depth at participant experience of following these diets, taking into account the many treatment-related barriers people face whilst undergoing chemotherapy, which are unique to this dietary intervention setting.

Each method is subject to its own limitations, however. The quantitative analysis forms a post-hoc analysis of secondary outcome data from a trial comparing IER to CER. As such, it is an exploratory analysis, where a large number of comparisons are made. Some of the associations seen may therefore represent chance findings due to multiple testing that require replication before they are assumed to reflect true associations. A further limitation is the lack of a control group in this trial. As previously discussed, this means the results pertaining to the IER can only be interpreted in reference to the CER, not to usual care.

The trial team chose to measure three behavioural change concepts in the quantitative analysis. The aim of including these concepts was to identify which concepts acted as barriers or facilitators to the intervention, in order to inform future trials. Although, as described in section 5.2.1.4, these have been found to be key concepts in previous dietary behaviour change research, providing a rationale for their inclusion, it is possible that other important concepts were not identified as part of this analysis, as they were not included in the trial questionnaires. For example, “goal setting” is a key construct in social-cognitive theory, and was utilised in the B-AHEAD 2 intervention delivery. Therefore, measurement of this concept could have provided useful data when evaluating whether the intervention was successful at targeting this specific concept. However, the use of qualitative methods to support the quantitative methods, means that there was also the opportunity to identify any key factors not initially identified during trial development.

No *a priori* adherence measure was defined in the protocol for B-AHEAD-2. Previous research has been found to use different methods to evaluate adherence or has not fully reported on this measure[265]. As such, there is no standard way to define adherence in dietary interventions, and a unique adherence measure was required and developed for this analysis. This definition aimed to create a measure, comparable between the two intervention arms, taking into account a margin of error for self-report measurement error. However, this meant that the adherence definitions used were reliant on self-reported dietary data. The limitations of using self-reported dietary data are well documented and include that it is subject to reporting bias and the potential for under-reporting, particularly in obese individuals, which can affect validity of results[279, 280]. As well as this, there was a large proportion of missing data within the diet diaries, as the adherence definition required all 7 days of the diary to be complete. To mitigate the limitations associated with the self-report data, the quantitative analysis also included weight change data, to be interpreted alongside the adherence data. The limitations associated with self-report data may explain, in part, why differences were seen in the analyses of the two measures. For example, the analysis identified predictors of adherence, but not of weight change. Alternatively, there may be an issue with statistical power due to small units of weight change being measured.

The framework approach was chosen for the qualitative analysis of the semi-structured interviews. As described in section 5.2.4.2, this was deemed an appropriate method to use due to its pragmatic and flexible approach to the analysis. However, one limitation with this method is that, when not conducted appropriately, it can miss out on providing rich data if an analytic narrative is not appropriately provided alongside interview excerpts, and the systematic nature of conducting the framework, means in-depth rich analysis can sometimes be missed[166, 228]. This potential pitfall with the framework method was attenuated in this analysis, as a subset of interview transcripts were independently coded by two researchers, then compared to ensure the interpretations were thoroughly explored and analysed in accordance with the original data. However, it should be acknowledged that other forms of qualitative analysis, such as Interpretative phenomenological analysis (IPA), could have also been used to interpret these data. IPA is a qualitative approach which aims to provide detailed examinations of the participants lived experience by interpreting how the participants make sense of their own personal experience. This means it is suited to the study of phenomenon which are complex and emotionally laden[281]. As the emotional aspect of dietary change was found to be a key concept in this analysis it provides evidence that other alternative methods of analysis, which focus on this, could be considered for future trials.

Within the qualitative analysis, it is possible that the study sample was not representative of the whole trial sample. An example of which is the fact that only one person was in the sub-group aiming to maintain their weight. This has implications for the generalisability of the results to the sample as a whole, as the findings may not represent the experiences of those in the weight maintenance group. For example, it is possible that there may have been different barriers and / or facilitators to dietary adherence between those who were aiming to lose weight compared to those who were aiming to maintain weight. This could affect the ability to extrapolate these findings to dietary interventions in other populations, where weight loss is not an aim of that intervention. For example, short-term fasting interventions are of interest in cancer populations where weight needs to be maintained, such as the colorectal cancer population in the SWiFT feasibility trial. Therefore, the inclusion of only one person in the maintenance group within this qualitative analysis limits the generalisability of the results to other short-term dietary restriction interventions in people for whom weight loss is not appropriate.

5.4.4 Implications for future research

Based on the findings of this study, the key factors to consider when designing a future trial of dietary restriction at the time of chemotherapy include, increasing support from partners or family members by including them in the intervention delivery, targeting emotional eating styles to aim to mitigate the potential negative effects of chemotherapy on eating, and including regular support from a dietitian to maximise adherence. However, limitations of the qualitative sample within this trial means that further research into the facilitators and barriers of interventions where weight loss is not a goal of the intervention, is still warranted.

In addition, dietary preferences were shown to be important and further research into the impact of dietary preferences on adherence may also help to further our understanding of how this affects adherence and outcomes within this setting. Using dietitian support to further tailor diets to participants dietary preferences, where required, may help to reduce the barriers of conflicting food preferences, identified in both intervention groups within this analysis. Researchers could also consider the potential for alternative trial designs to take into account the role that dietary preferences have on motivation to adhere to the diets. Alternatively, training researchers to explore preferences in more depth and challenge stated preferences could be considered, to help reduce the impact of predefined preferences on recruitment and adherence to interventions.

The effect of the interventions on self-efficacy is still unclear. Including a control group in future trials will provide further information about how effective these interventions are at inducing behaviour change, in relation to this concept in particular.

5.4.5 Summary

The overall goal of the B-AHEAD 2 trial was to assess whether IER was more effective than CER in preventing weight gain in normal weight women and promoting weight loss in overweight women during chemotherapy[233].

This analysis has provided insight into the effect of the interventions on some common behavioural change concepts and their relationship with adherence and weight loss among women undergoing two different dietary restriction interventions at the time of chemotherapy for breast cancer. However, it was not possible to fully assess whether changes in behavioural scores were caused by the interventions due to the lack of a control group, and further work is needed to fully understand the impact of the interventions on behavioural change.

Some facilitators and barriers were identified that can be targeted in future interventions to improve adherence, with the ultimate aim of maximizing effectiveness of these dietary interventions.

Key Messages

1. The B-AHEAD 2 trial aimed to assess whether IER was more effective than CER in preventing weight gain in normal weight women and promoting weight loss in overweight women during chemotherapy.
2. This analysis aimed to assess the feasibility of adhering to dietary restriction interventions during chemotherapy, by synthesising quantitative behavioural change data and qualitative interview data and to identify differences in adherence between the two intervention groups.
3. Changes in behaviour concept scores from baseline to end of trial were broadly similar between the two groups, and there were no differences in concept scores between groups at the end of the trial.
4. There was an increase in perceived behavioural control, habit and automaticity and restrained eating style, from baseline to end of trial.
5. There was a reduction in external and emotional eating styles from baseline to follow-up.

6. Perceived behavioural control appeared to have improved during the intervention, though total self-efficacy scores remained unchanged.
7. Baseline self-efficacy score predicted adherence in both intervention groups, while baseline external and emotional eating style scores also predicted adherence in the IER group.
8. Change in habit and automaticity scores from baseline to end of trial were associated with weight loss in the CER group.
9. Further research into the impact of chemotherapy on dietary self-efficacy in usual diet conditions, may help to understand the impact of treatment on this measure, and identify how it can be targeted further in future trials, to induce dietary change.
10. The strongest facilitator identified in the qualitative analysis was the support provided from the dietitian.
11. The main barrier to adherence was the conflict between personal dietary preferences and the prescribed diets.
12. A complex relationship existed between social support and dietary adherence, with social influences identified as a facilitator within the CER group, but a barrier in the IER group.
13. Including partners or family members in the intervention delivery, particularly, in trials of IER may help to utilize social support as a potential strategy to improve adherence.
14. Targeting a reduction in emotional eating may also be a key factor to intervention success, particularly in people receiving chemotherapy, which affects physical and mental wellbeing.

Chapter 6 DISCUSSION

6.1 INTRODUCTION

The aims of this thesis were to systematically review the literature on dietary restriction at the time of chemotherapy, to develop and test the feasibility of a short-term fasting intervention in people undergoing chemotherapy for colorectal cancer and to explore the feasibility of adhering to energy restriction diets at the time of chemotherapy for breast cancer.

To achieve this, three studies were conducted. Firstly, a systematic scoping review of the literature was conducted, with the aim of providing an overview of the research to date into dietary restriction at the time of cancer treatment, and to identify gaps in the literature. Secondly, a feasibility Randomised Controlled Trial (RCT) to test the feasibility of implementing a 36-hour short-term fast prior to Capecitabine Oxaliplatin (CAPOX) chemotherapy for colorectal cancer was designed and is currently open to recruitment. Finally, quantitative behavioural change and qualitative interview data from a previous RCT of intermittent energy restriction compared to continuous energy restriction in women receiving chemotherapy for breast cancer were analysed and synthesised in a mixed method study, to assess the feasibility of adhering to the dietary interventions in this group during treatment.

Each of these studies were carried out using a pragmatic methodology which has allowed the work to draw on multiple research methods and forms of data to add to the body of evidence on the feasibility of implementing dietary restriction interventions during cancer treatment.

This chapter will summarise the main findings from each project, discuss the implications of these findings for both future research and clinical practice and, finally, discuss the strengths and weaknesses of the thesis.

6.2 SUMMARY OF MAIN FINDINGS

The main findings from this thesis are summarised below. These have been grouped under three headings, which reflect different aspects of assessing the feasibility of dietary restriction interventions. These are: recruitment to dietary restriction interventions during cancer treatment, adherence to dietary restriction interventions during cancer treatment and facilitating behaviour change within this setting.

6.2.1 Recruitment to dietary restriction interventions during cancer treatment

The scoping review described in chapter 3 found that few studies have been published to date on dietary restriction during treatment for cancer, and that the majority of these have been studies of ketogenic diets. Recruitment to trials is often hard to assess due to lack of reporting on recruitment processes, including the number of people assessed for eligibility[282]. Within the scoping review, only one trial of dietary restriction reported their overall recruitment rate. However, four studies were stopped early due to low recruitment. This suggests participant recruitment may be an issue in trials of dietary restriction, though without improved reporting from trials, this is difficult to confirm. This paucity of data meant that further research, such as the SWiFT feasibility RCT described in chapter 4, was warranted, to assess whether future large multi-site trials are feasible. SWiFT will aim to address this gap in the literature, by providing data on the likely recruitment to any planned large trial.

The published scoping review and subsequent update found that more studies continue to be registered in trial databases, and that the range of forms of dietary restriction being studied is also increasing. This confirms that dietary restriction remains an area of active research interest.

During the initial set-up of the SWiFT trial (chapter 4), the proportion of sites that accepted the offer to open the trial to recruitment was low. Feedback on reasons for declining to open the trial identified uncertainty around the ability to recruit to the trial and concerns about asking participants to fast, as the barriers to opening sites to recruitment. Within the UK, NHS sites are required to submit performance data on trial recruitment to the National Institute for Health Research (NIHR), including whether they have delivered the trial to time and target. These data are made publicly available which allows comparisons of performance between sites and ultimately aims to increase the number of people who participate in research[283]. However, this can also reduce the incentive for sites to open trials which could be perceived as being more difficult to recruit to, as these could impact negatively on performance metrics. Depending on the findings, data from trials such as SWiFT may provide reassurance that recruitment is feasible, which could increase the willingness of sites to participate in future trials of dietary restriction during cancer treatment. Lessons learned from SWiFT could also be used to refine and maximise recruitment strategies for a larger definitive trial, should it be warranted.

Taken together, these findings suggest that recruitment may be an issue for trials of dietary restriction interventions. Although there are plausible biological mechanisms behind the potential benefits of dietary restriction at the time of chemotherapy which have been identified through cell line and animal

models, it is still not clear how well these findings translate to humans. As the potential efficacy of interventions relies on people being willing to undertake the fast, issues with recruitment will need to be addressed if full scale, adequately powered trials are to be carried out to assess the efficacy of these interventions.

6.2.2 Adherence to dietary restriction interventions during cancer treatment

As identified in the systematic scoping review (Chapter 3), overall, studies of dietary restriction interventions to date have found that participants are able to tolerate the interventions in terms of safety, with only mild and transient side effects reported in the majority of interventions. Without clearer reporting on recruitment rates and strategies, however, it is unclear whether these results reflect a self-selected group who are able to tolerate dietary restriction. As well as this, levels of adherence to the interventions have been variable, and often low, with less than half of participants adhering to the diets, in some cases. For example, two of the six ketogenic diet interventions were terminated due to poor recruitment and adherence, while adherence in the remaining trials which reported on this measure ranged from 40-80%. Similarly, the most recent trial of a fasting mimicking diet found that two thirds of participants were not compliant for half of the cycles[195]. This suggests issues with adherence may be related to something other than side effects caused by the interventions themselves. As discussed in further detail throughout this chapter, many potential reasons for non-adherence to dietary restriction interventions during cancer treatment have been identified in this thesis. These include the palatability of diets and how they align with people's dietary preferences, the potential for the physical and emotional side effects of chemotherapy to hinder adherence as well as the potential for low social support to follow dietary restrictions at a time when adequate nutritional intake is considered important. Further research into why adherence can be low is required, to identify reasons for poor adherence so that future interventions can be designed to ameliorate this issue.

For example, within the B-AHEAD 2 trial of continuous versus intermittent energy restriction during chemotherapy for breast cancer, adherence was found to be lower than in trials of these interventions in populations not receiving cancer treatment. As discussed in chapter 5, this may be due to inconsistencies in definitions of adherence between trials but could also be due in part to the additional burden of chemotherapy which participants are experiencing at the time of dietary intervention. These include treatment side effects and the emotional burden of treatment. Analysis of the motivating

factors for taking part in the trial identified that key reasons for enrolling into the trial were the need for something to focus on during treatment, and the hope that the intervention would be a distraction from the chemotherapy. Similar to this, previous research has identified that the additional feelings of control that following a diet can provide may increase perceptions of agency during cancer treatment, adding benefit to participants at a time when perceived agency and control can be low[284, 285]. However, the analysis also identified that some participants struggled to maintain the diets within the chemotherapy setting. These findings indicate that there is a juxtaposition when implementing dietary interventions during cancer treatment, between the potential for interventions to offer a level of control to people who might feel in need of it during this time, but also the potential to put additional burden on people at a time when they are already burdened by treatment. This needs to be carefully balanced within trials of dietary interventions. Potential ways to do this may include targeting barriers and facilitators to facilitate behaviour change which are discussed in more detail below.

6.2.3 Facilitating behaviour change

Although behaviour change theory has been found to improve effectiveness of dietary interventions in areas such as diets for cancer prevention[123], it is less clear how theory could be applied to dietary restrictions implemented during cancer treatment. This is because diets for cancer prevention tend to target long-term behaviour change, while interventions during cancer treatment only require short-term behaviour change. Also, people following dietary restriction during cancer treatment are contending with the additional physical and emotional effects of their treatment.

One important aspect of understanding the behaviour change process within interventions includes identifying both barriers and facilitators to intervention adherence. The potential barriers and facilitators identified within this thesis are summarised below, and how these may apply to theories for use in future interventions is discussed.

6.2.3.1 Removing barriers to dietary restriction adherence

One of the main barriers identified in the qualitative analysis of B-AHEAD 2 was the dissonance that sometimes occurred between participants' personal dietary preferences and their prescribed diet, in both the continuous and intermittent energy restriction arms. However, examples of preferences given were varied, so further research may be required to identify if patterns exist in types of food or food

groups which are particularly important. This was also identified as potential issue to adherence to the fasting mimicking diet in the systematic review, where non-adherence to the diet was attributed to palatability of the diet. As discussed in chapter 5, changes in perception of foods during chemotherapy, may make this a particularly important barrier for dietary restriction interventions that are implemented during cancer treatment.

Analysis of the B-AHEAD 2 trial data also identified emotional eating as a key behavioural concept which could act as a barrier to intervention adherence. Emotional eating has been found to lead to overconsumption of food and to be associated with being overweight[264]. Chemotherapy for breast cancer is known to produce psychological distress as well as functional impairment[286], while chemotherapy side effects may affect physical, emotional, and social well-being in people receiving chemotherapy for colorectal cancer[287]. Emotional eating may therefore be a barrier of particular importance within the chemotherapy setting. The interventions used in B-AHEAD 2 resulted in a reduction in emotional eating style in both intervention groups through provision of information on how to i) gain control of eating habits ii) deal with cravings, and iii) avoid using food as a reward system. Continuing to utilise these techniques in future research and continuing to try to alter emotional eating styles may improve adherence, by reducing this potential barrier.

Finally, low dietary self-efficacy, a person's beliefs about their ability to influence aspects of their life[285], was another behavioural concept identified as a potential barrier to adherence in the qualitative analysis of B-AHEAD 2. The quantitative analysis suggested that total self-efficacy did not increase during the intervention, despite this concept being targeted during the intervention delivery. The lack of a control group in the trial design means it is not possible to fully assess the effect of the interventions on self-efficacy. The results could signify that the intervention was not successful at improving self-efficacy. Alternatively, they could indicate that the intervention allowed women to maintain their level of dietary self-efficacy, when it might otherwise have been reduced. As discussed above, a cancer diagnosis and the treatment which follows is associated with a loss of control, and similarly can lead to a reduction in self-efficacy. As increasing self-efficacy has been found to be an effective way to alter health related behaviours such as diet[242], it suggests that targeting this concept in future trials of dietary restriction during chemotherapy could lead to improved adherence to dietary restriction interventions.

6.2.3.2 Maximising facilitators of dietary restriction adherence

Ongoing contact with the trial dietitian was identified as a facilitator to adherence in B-AHEAD 2. Although, qualitative data from SWiFT has yet to be analysed, feedback from the initial participant interview suggested that contact from the research team during the fasting period of each cycle would have been beneficial. The participant felt that this would have provided reassurance and support while they were trying to implement the short-term fast. The findings from B-AHEAD 2 and the initial feedback from SWiFT both support those from previous research, that regular contact and support improves adherence[276]. Due to the differing lengths of the interventions included in these trials, it also suggests that this may be an important facilitator to adherence, even when interventions are implemented for shorter periods.

Social support may also be key to maximising adherence as it was found to act as a barrier in the intermittent restriction group, and a facilitator in the continuous energy restriction group. Previous research into diet following cancer diagnosis and treatment has also identified the important role that family members and partners play in terms of food choice and preparation[285, 288]. As partners often act as gatekeepers to food provision during times of poor health, by providing or cooking food, they may be ideally placed to maximise adherence. Conversely, social influences were identified as a barrier in the intermittent energy group. Therefore, there may be a need to include partners or family members in the delivery of dietary interventions, with the aim of increasing their understanding of the intervention requirements and the potential benefits of the diet. During intervention delivery, the research participant is essentially trained in the diet and provided with literature on how to apply the diet. However, it may be that partners and family members take the lead in food provision at this time. Therefore, providing them with the same training and educational material could optimise adherence. In this way the role of family members as gatekeepers of food provision could be better utilised by empowering them to provide both social support and, more practically, food that is compliant with the diet.

6.2.3.3 Identifying behaviour change theory to inform future interventions

As discussed in chapter 2, identifying which behaviour change theories may be useful in intervention design and delivery is of interest in dietary restriction interventions. This is due to the fact that dietary restriction interventions in relation to cancer treatment can differ from other forms of dietary intervention, due to the short-term nature of the behaviour change that is taking place, and the particular barriers faced by people receiving cancer treatment. The B-AHEAD 2 interventions differed

from some other dietary restriction interventions because participants were asked to follow the diets throughout their entire course of chemotherapy treatment rather than, for example, over a 24–72-hour period covering each chemotherapy administration. So, although not directly applicable to short-term fasts, findings from B-AHEAD 2 could provide an understanding of the barriers and facilitators which people face when undertaking restriction during this time. This could then be used to inform other forms of restriction, such as short-term fasts or fasting mimicking diets.

As discussed previously here, and in further detail in chapter 5 (section 5.4), self-efficacy, emotional eating, dietitian contact and social support stood out as concepts of interest due to their potential to act as barriers or facilitators to adherence. The identification of some of the barriers and facilitators to dietary restriction within this particular setting i.e. cancer treatment, can help inform the selection of a theoretical framework that would be considered to most likely to influence these factors[289]. A number of behavioural change theories include aspects of these concepts and measures. For example, Social Cognitive Theory is a commonly used behaviour change theory for dietary interventions in people with cancer[126]. This theory proposes that behaviour is influenced by a range of personal, environmental, and behavioural factors. Self-efficacy is a key behavioural factor, while social influences are captured within environmental factors, also described as external social context [127]. Another behaviour change theory, The Trans-Theoretical Model, suggests that behaviour change requires a progression through six stages of change which can be influenced by factors such as decisional balance, self-efficacy, and temptations [128]. As some of the constructs included in these models were identified as concepts of interest in this thesis, it provides a rationale for using these models in future intervention design, as it suggests that these theories may be most applicable to dietary interventions implemented during cancer treatment. Theories such as the Social Cognitive Theory and the Trans-Theoretical Model could then be used in future design to understand other factors, not identified in this body of research, which may influence short-term dietary change, and help to identify techniques that could be used to alter these factors. Constructs from behaviour change theories such as these can be applied within intervention design, by helping to establish both the content of the intervention and its mode of delivery, to target the key concepts, with the aim of maximizing intervention adherence. For example, provision of training and regular goal setting can be applied to aim to improve self-efficacy or identified barriers such as emotional eating can continue to be targeted through educational or motivational material to reduce their impact[290].

6.3 IMPLICATIONS FOR FUTURE RESEARCH

Each of the findings described above help to inform future research, by providing implications and recommendations for future trials of dietary restriction interventions at the time of cancer treatment. The findings and their subsequent implications and recommendations for future research are summarised in Table 6-1 below.

*Table 6-1: **Summary of the main findings and their implications for future trials of dietary restriction interventions during cancer treatment***

Key Finding	Implications for Research	Recommendations for Future Research
Low agreement to take on the trial of a short-term fasting intervention by NHS sites.	• If issues with recruitment are identified through feasibility trials such as SWiFT, it will provide the opportunity to address these issues with the aim of improving rates for future trials. • If recruitment rates are acceptable, data can be used to encourage further sites to open in adequately powered efficacy trials.	• More pilot/feasibility research is warranted, building on the findings of research conducted to date. • Future trials should ensure data on feasibility outcomes, such as recruitment rates and tolerability, are collected and openly reported in detail.
Potential issues with participant recruitment to trials of dietary restriction during cancer treatment.	• Delays to opening SWiFT due to the COVID-19 pandemic means it has not been possible to fully assess feasibility of recruiting to a short-term fasting intervention. • However, the systematic scoping review identified the potential for recruitment to be an issue in trials of dietary restriction, so the possibility	• Further research into why people decline to participate is warranted. • Qualitative work can be used if routine screening data is not informative. • Qualitative research interventions for recruiters, aimed at improving recruitment and challenging dietary preferences should also be considered.

	must be considered when planning future trials.	
Adherence to interventions of dietary restriction during cancer treatment can be low.	• Further research into factors that affect adherence is warranted. • Factors affecting adherence that have been identified in this thesis (outlined below) should be considered when designing future intervention delivery.	• Factors that act as barriers and facilitators, identified in this thesis, provide a rationale for using behaviour change theories such as Social Cognitive Model and Trans-Theoretical Model to inform future intervention design.
Dietary preferences are a barrier to dietary adherence.	• This may be particularly important in dietary restriction interventions implemented during cancer treatment, because of the effects of treatment on food perception.	• Intervention delivery should include strategies for coping with taste changes. • Future research can be used to identify patterns in food preferences e.g., are higher carbohydrate or lower dairy options important? • Future interventions could also aim to provide flexibility in diet content in order to allow for changes in food perception during treatment.

Low self-efficacy is a barrier to dietary adherence.	• Although self-efficacy was identified as a barrier, analysis of B-AHEAD 2 data did not allow for assessment of the effect of the dietary interventions on this measure due to the lack of a control group. • Further understanding of the impact of cancer treatment on dietary self-efficacy is required.	• Future trials should include a control group to fully assess the impact of interventions on self-efficacy. • If self-efficacy is found to be significantly impacted by treatment, future research should aim to identify ways to increase dietary self-efficacy during chemotherapy, drawing on behaviour change theory to design interventions.
Emotional eating is a barrier to dietary adherence	• This is a barrier of interest, particularly during chemotherapy, due to the negative impact of treatment on emotional wellbeing.	• Future interventions should continue to include educational material on how to cope with emotional eating, to combat poor adherence, using techniques such as those outlined in the B-AHEAD 2 trial.
Dietitian contact is a facilitator of adherence.	• Implementing this in future trials has an implication on the cost of intervention delivery, due to research staff time spent supporting participants.	• Regular dietitian or research team contact in future trials may help to facilitate adherence to interventions, including those involving short-term restriction.

		• Further research into how best to deliver support could be used to identify whether lower cost options provide similar benefit. For example, Discreet Choice Experiments could be used to identify participant preferences on how they receive contact[291, 292], with the aim of designing interventions that balance cost with participant preference.
A complex relationship exists between social support and dietary adherence, where it can act as either a barrier or a facilitator to adherence.	• This may be of particular importance for more restrictive diets, which go against colloquial knowledge of feeding to increase energy during times of ill health and when family members are likely to have concerns over adequate nutrition intake.	• Including partners or family members in the intervention delivery, by providing them with training on the diet and literature on the potential benefits of the diet, may help to maximise the benefits of social support, while reducing the likelihood of family members acting as barriers to adherence.

6.4 IMPLICATIONS FOR CLINICAL PRACTICE

As the focus of this thesis was on the feasibility of implementing interventions of short-term dietary restriction, with the aim of informing future research, most of the implications of this research apply to the design and delivery of future trials. However, there is a potential implication for clinical practice that relates to patient's dietary choices at the time of chemotherapy. One study identified in the systematic scoping review recruited people who had chosen to fast as part of their cancer treatment, outside of a trial setting[190]. In addition to this, the research conducted in animal models and early-stage trials has received media attention[293-295]. Consequently, it is possible that interest in dietary restriction to try to improve side effects and treatment efficacy will lead some people to alter their diet during treatment. This has implications for clinical practice as it suggests there needs to be an awareness amongst healthcare providers of the current evidence on these forms of restrictions, so that they are able to discuss the evidence base and potential benefits and disadvantages of dietary restriction with patients, when approached about the topic by their patients.

6.5 STRENGTHS AND WEAKNESSES

This thesis drew on three studies which each looked at different aspects of feasibility of dietary restriction interventions during treatment for cancer. This allowed a range of data to be drawn together to assess the feasibility of implementing dietary restriction interventions at this time. Taken together, the three projects have provided an overview of what the research to date has shown, identified how issues with recruitment and adherence may affect feasibility of trials, and made recommendations on how future trials could aim to overcome some of the issues identified. Using mixed methods research to explore the feasibility of dietary restriction interventions during cancer treatment, also provides the opportunity to look at feasibility in an holistic manner. It provides an insight into both the elements that can be quantitatively measured, such as recruitment, retention and adherence rates, whilst also allowing more in-depth exploration of participant experiences, such as acceptability and tolerability of the interventions and barriers to adherence.

The scoping review that was conducted to review the literature on dietary restriction during cancer treatment was conducted in a systematic manner to a set of *a priori* defined search criteria and outcomes of interest. These were made publicly available prior to initiating the review. This ensured transparency and provided assurance that the findings have been reported in full. However, the paucity of data and the heterogeneity of interventions and reporting of feasibility findings, means that a meta-

analysis of the findings was not possible. The review could not, therefore, definitively answer the question of whether dietary restriction interventions are feasible or efficacious. It did, however, identify potential issues of recruitment and adherence, that can impact feasibility, and highlighted the importance of clear reporting on these factors.

The SWiFT feasibility RCT that was developed to test the feasibility of a 36-hour short-term fast prior to chemotherapy for colorectal cancer is a well-designed RCT which should produce high quality data on the feasibility of this intervention. It also made use of patient and public involvement to inform the design of the intervention and patient literature, to increase acceptability of the intervention design and delivery. However, the delays to opening the trial to recruitment due to the COVID-19 pandemic, mean that the feasibility could not be fully assessed and reported on within this thesis.

To further explore the feasibility of dietary interventions during cancer treatment, in lieu of the results from SWiFT, data from the B-AHEAD 2 trial were analysed. This was the first trial comparing intermittent to continuous energy restriction during cancer treatment. As such, it was able to provide unique insights into the barriers and facilitators experienced by people undertaking dietary restriction at this time and whether the interventions were able to incite behaviour change. However, the lack of a control group for comparison meant it was not possible to fully assess the effect of the interventions on behaviour change, and further research will therefore be required. Moreover, this trial included a different patient population to SWiFT, and each population may face challenges that are unique to their cancer type and treatment pathway. For example, in SWiFT participants undergo the intervention following recent colorectal surgery. This could impact their interest in enrolling into a dietary intervention and/or their ability to follow the intervention. Particularly if they continue to experience issues with digestion following surgery.

Due to the variety of forms of dietary restriction summarised in this thesis, some findings may not apply to all forms of intervention. For example, the findings from the behaviour change analysis of B-AHEAD 2 data are from a dietary intervention implemented over the entire course of chemotherapy, so may not be directly applicable to other forms of restriction such as short-term fasts which are implemented over 24-72 hours around the time of chemotherapy administration. However, these findings provide a framework from which similar methods can be implemented in future studies of short-term restrictions, where the applicability of findings from B-AHEAD 2 to short-term restriction can subsequently be fully assessed. For example, analysis of B-AHEAD 2 has identified ways that the design of SWiFT could have been improved. Firstly, increased contact from the research team during the short-term fast could

provide additional support to participants when fasting. Secondly, targeting self-efficacy through participant literature and during intervention delivery may have been of benefit. Thirdly, acknowledging that emotional eating may be a barrier and providing participants with the knowledge of how to avoid this form of eating style could benefit adherence. Finally, including interviews with people who decline to take part in SWiFT, would have provided the opportunity to explore reasons for declining the trial, which might not be otherwise captured through traditional trial screening logs.

The diverse range of forms of dietary restriction currently being studied also means that meta-analyses of findings have not been possible, due to heterogeneity in interventions and outcomes. This is likely to continue to be an issue, as further forms of intervention continue to be studied, as identified in the systematic scoping review.

Finally, though assessing the feasibility of dietary restriction interventions allows for an understanding of whether definitive trials can be conducted, it does not answer the question of whether these interventions reduce chemotherapy related toxicities. In identifying and addressing issues with feasibility, however, this body of work can inform future trials so that recruitment and adherence can be maximised in RCTs to assess efficacy of dietary restriction interventions.

6.6 CONCLUSION

This thesis aimed to assess the feasibility of implementing dietary restriction interventions at the time of cancer treatment. This is an area of growing research interest, due to pre-clinical findings in cell line and animal models showing the potential for dietary restriction, such as short-term fasting to reduce the toxicities associated with cancer treatments.

The findings from this body of work show that the research in humans to date is limited, and issues surrounding recruitment to trials and adherence to interventions may impede the process of testing the efficacy of dietary restriction interventions. As such, further research should focus on identifying barriers to recruitment and improving adherence, to maximise the likelihood of being able to test these interventions in adequately powered trials.

This thesis was not able to provide data on the feasibility of a short-term fasting intervention, as was set out in the aims. However, it has identified that, across other studies, recruitment and adherence are factors which may influence feasibility. It has also identified potential barriers and facilitators of

adherence using data from a previously conducted trial of intermittent compared to continuous energy restriction during breast cancer treatment.

Finally, it is acknowledged that, although evidence of efficacy of dietary restriction is limited, there is a growing interest from research communities and people receiving cancer treatment alike. Addressing issues with feasibility is therefore important to ensure that the efficacy of dietary restriction can be fully assessed in future studies, allowing healthcare providers and people receiving chemotherapy to make informed choices on whether to implement dietary restriction during cancer treatment.

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Appendix A – Systematic scoping review search terms used in the Medline database search

1. Fasting/

2. (diet* adj2 restrict*).tw,kf.

3. (calorie* adj2 restrict*).tw,kf.

4. (intermittent* adj2 fast*).tw,kf.

5. Starvation/

6. ketogenic diet.tw,kf.

7. exp Ketone Bodies/

8. ((protein or carbohydrate) adj2 restrict*).tw,kf.

9. "atkins diet".tw,kf.

10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11. Neoplasms/

12. cancer*.tw,kf.

13. carcinoma*.tw,kf.

14. tumor*.tw,kf.

15. tumour*.tw,kf.

16. sarcoma*.tw,kf.

17. malignan*.tw,kf.

18. oncolog*.tw,kf.

19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. 10 and 19

21. animals/ not humans/

22. exp Animals, Laboratory/

23. exp Animal Experimentation/

24. Models, Animal/

25. Rodentia/

26. (rat* or mouse or mice).ti.

27. 21 or 22 or 23 or 24 or 25 or 26

28. 20 not 27

Trial Name: SWiFT Site Code: __ __ Participant ID: __ __

CRF 3: Chemotherapy Cycle 1 Day 1 visit

VISIT DETAILS	
1. Visit Date (dd/m/yyyy)	__ __ / __ __ / __ __ __ __
DEXAMETHASONE ADMINISTRATION	
Dexamethasone dose	__ mg
Time taken (24hr)	__ __:__ __
PHYSICAL EXAMINATION	
Weight	__ __ __ . __ (kg)
Blood Pressure	__ __ __ / __ __ __(mmHg)
Hand Grip Strength ***(Repeat 3 times - required at cycle 3 only)***	1st __ __ (kg) 2nd __ __ (kg) 3rd __ __ (kg)

ECOG Performance status *Select one*	☐$_0$ Fully active, able to carry on all pre-disease performance without restriction ☐$_1$ Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work ☐$_2$ Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours ☐$_3$ Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours ☐$_4$ Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

ADDITIONAL BLOOD TESTS:	
Please complete the following using additional blood samples taken immediately prior to chemotherapy administration:	
CRP (mg/L)	
Glucose (mmol/L)	
Insulin (mIU/mL)	

Has an additional blood sample been collected for metabolic analysis? ☐$_1$ Yes ☐$_2$ No

If YES

Time collected (24hr)

__ __:__ __

Date collected (dd/m/yyyy)

__ __ / __ __ / __ __ __ __

If NO

Reason not collected:

_____

_____

_____

Investigator name (print): _____ Investigator signature: _____

Date Completed (dd/mm/yyyy): __ __ / __ __ / __ __ __ __

SWiFT CRF 3 V2, 25.11.19

Appendix C – SWiFT Interview Topic Guide – Intervention Group

Introduction

Introduce self and thank patient for talking to me

Recap on study

We are conducting a study looking at the experiences of …..

Ensure confidentiality and that we can stop at any time

Ask if they have any questions before we start?

Confirm they are happy to start the interview and start audiorecording

If telephone interview, explain that you will ask them to confirm again that they give consent to take part in the interview once the audiorecorder is switched on.

Their role in the trial

Could you tell me about your treatment plan?

You agreed to take part in the SWiFT trial, what were you asked to do as part of the trial?

(to confirm which arm they were randomised to)

Why did you agree to take part in this trial?

Experience of fasting

How would you describe your overall experience of fasting?

Did you feel any positive effects of fasting?

Did you feel any negative effects of fasting?

How easy or difficult did you find fasting?

Would you change any elements of the fast e.g. length, the amount/type of food you were allowed to have?

Were there any issues which stopped you being able to complete the fast?

If so, what might have helped you to overcome these issues?

Have you had any more cycles of chemotherapy since finishing the trial?

(to ascertain tense of the next question)

Did you/do you plan to continue fasting on any subsequent cycles you have/had?

Data collection

How did you get on with using the web/app based systems to report side effects?

How did you find using the food log?

Chemotherapy and Diet

Did the side effects of chemotherapy change the amount/type of food you ate?

If so, in what way?

Did you receive any advice about what kind of food to eat during treatment?

If so, what advice and from who?

Appendix C – SWiFT Interview Topic Guide – Control Group

Introduction

Introduce self and thank patient for talking to me

Recap on study

We are conducting a study looking at the experiences of …..

Ensure confidentiality and that we can stop at any time

Ask if they have any questions before we start?

Confirm they are happy to start the interview and start audiorecording

If telephone interview, explain that you will ask them to confirm again that they give consent to take part in the interview once the audiorecorder is switched on.

Their role in the trial

Could you tell me about your treatment plan?

You agreed to take part in SWiFT, what were you asked to do as part of the trial?

(to confirm which arm they were randomised to)

Why did you agree to take part in this trial?

Experience of the "Control Arm"

Did you change the amount/type of food you ate before your chemotherapy cycles in any way?

How did you get on with using the web/app based systems to report side effects?

Chemotherapy and Diet

Did the side effects of chemotherapy change the amount/type of food you ate?

If so, in what way?

Did you receive any advice about what kind of food to eat during treatment?

If so, what advice and from who?

Appendix E – B-AHEAD 2 Baseline Eating and Exercise Questionnaire

Questionnaire:

Eating and Exercise Patterns

1. My views about weight control during treatment

We are interested in what you think about a number of aspects of your weight. Please indicate what you think about your weight by ticking one of the statements below:

☐ I do not think that my current weight is a problem for my health

☐ I think that my current weight is a problem for my health.

Many women with breast cancer gain weight during treatment. We are interested in what you think about weight gain. Please read the statements below and make a mark to indicate how much you agree with each statement. Please answer all questions.

1. If I gain weight during treatment it will be mainly because of my diet and exercise behaviors.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

2. I believe controlling my weight during treatment will reduce the chances of my breast cancer re-occurring.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

3. I believe I will be able to maintain my current weight during treatment.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

4. I will probably gain weight during treatment whatever I do.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

5. Controlling my weight during treatment is largely dependent upon myself.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

6. My ability to control my weight during treatment will be limited by my treatments and medications.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

2. Habits

Please read the statements below and circle a number to indicate how much you agree with each statement. Please answer all questions.

Watching my diet is something…

	Strongly Disagree	Mostly Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Mostly Agree	Strongly Agree
1. I do automatically	1	2	3	4	5	6	7
2. I do without having to consciously remember	1	2	3	4	5	6	7
3. I do without thinking	1	2	3	4	5	6	7
4. I start doing before I realise I'm doing	1	2	3	4	5	6	7

Exercising regularly is something…

	Strongly Disagree	Mostly Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Mostly Agree	Strongly Agree
1. I do automatically	1	2	3	4	5	6	7
2. I do without having to consciously	1	2	3	4	5	6	7
3. I do without thinking	1	2	3	4	5	6	7
4. I start doing before I realise I'm doing	1	2	3	4	5	6	7

3. How confident are you that you can resist over eating or eating unhealthily in the following situations

Please read the statements below and circle a number to indicate your answer. Please answer all questions.

	Not at all confident	Slightly confident	Quite confident	Very confident	Extremely confident
1) I can resist over eating or eating unhealthily when I am anxious (nervous)	1	2	3	4	5
2) I can resist over eating or eating unhealthily when I am depressed (or down)	1	2	3	4	5
3) I can resist over eating or eating unhealthily when I am angry (or irritable)	1	2	3	4	5

4) I can resist over eating or eating unhealthily when I have experienced failure	1	2	3	4	5
5) I can resist over eating or eating unhealthily when I am bored	1	2	3	4	5
6) I can resist over eating or eating unhealthily when I am thinking negatively about my appearance	1	2	3	4	5
7) I can resist over eating or eating unhealthily when I am worrying about my future health.	1	2	3	4	5
8) I can control my over eating or eating unhealthily on the weekends	1	2	3	4	5
9) I can resist over eating or eating unhealthily when there are many different kinds of food available	1	2	3	4	5
10) I can resist over eating or eating unhealthily even when I am eating out or at a party	1	2	3	4	5
11) I can resist over eating or eating unhealthily even when high-calorie foods are available	1	2	3	4	5
12) I can resist over eating or eating unhealthily even when I have to say 'no' to others	1	2	3	4	5
13) I can resist over eating or eating unhealthily even when I feel it's impolite to refuse a second helping	1	2	3	4	5
14) I can resist over eating or eating unhealthily even when others are pressuring me to eat.	1	2	3	4	5
15) I can resist over eating or eating unhealthily even when I think others will be upset if I don't eat	1	2	3	4	5

16) I can resist over eating or eating unhealthily when I feel physically run down	1	2	3	4	5
17) I can resist over eating or eating unhealthily when I am in pain	1	2	3	4	5
18) I can resist over eating or eating unhealthily when I feel uncomfortable	1	2	3	4	5

Are you still having regular menstrual cycles? If yes please answer question 19. If no please go to question 20

	Not at all confident	Slightly confident	Quite confident	Very confident	Extremely confident
19) I can resist over eating or eating unhealthily in the week before a period	1	2	3	4	5
20 - 23) Skip to question 24					
24) I can resist over eating or eating unhealthily when I have disrupted sleep patterns	1	2	3	4	5
25) I can resist over eating or eating unhealthily when I am tired	1	2	3	4	5
26) I can resist over eating or eating unhealthily when I feel nauseous	1	2	3	4	5
27) I can resist over eating or eating unhealthily when my sense of taste is altered	1	2	3	4	5
28) I can resist over eating or eating unhealthily when I don't have time to think about my diet	1	2	3	4	5
29) I can resist over eating or eating unhealthily when I have nothing to do	1	2	3	4	5
30) I can resist over eating or eating unhealthily when I am outside my normal routine	1	2	3	4	5

31) I can resist over eating or eating unhealthily when I am watching TV	1	2	3	4	5
32) I can resist over eating or eating unhealthily when I am reading	1	2	3	4	5
33) I can resist over eating or eating unhealthily just before going to bed	1	2	3	4	5
34) I can resist over eating or eating unhealthily when I am happy	1	2	3	4	5

4. My eating style

This section asks about your eating style. Please read the statements below and make a mark to indicate how much you agree with each statement. Please answer all questions.

	Never	**Rarely**	**Some times**	**Often**	**Almost Always**
1. When you have put on weight do you eat less than you usually do?	☐	☐	☐	☐	☐
2. Do you have a desire to eat when you are irritated?	☐	☐	☐	☐	☐
3. If food tastes good to you, do you eat more than usual?	☐	☐	☐	☐	☐
4. Do you try to eat less at mealtimes than you would like to eat?	☐	☐	☐	☐	☐
5. Do you have a desire to eat when you have nothing to do?	☐	☐	☐	☐	☐

	Never	Rarely	Some times	Often	Almost Always
6. If food smells and looks good, do you eat more than usual?	☐	☐	☐	☐	☐
7. How often do you refuse food or drink offered because you are concerned about your weight?	☐	☐	☐	☐	☐
8. Do you have a desire to eat when you are depressed or discouraged?	☐	☐	☐	☐	☐
9. If you see or smell something delicious, do you have a desire to eat it?	☐	☐	☐	☐	☐
10. Do you watch exactly what you eat?	☐	☐	☐	☐	☐
11. Do you have a desire to eat when you are feeling lonely?	☐	☐	☐	☐	☐
12. If you have something delicious to eat, do you eat it straight away?	☐	☐	☐	☐	☐
13. Do you deliberately eat foods that are slimming?	☐	☐	☐	☐	☐
14. Do you have a desire to eat when somebody lets you down?	☐	☐	☐	☐	☐
15. If you walk past the baker do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
16. When you have eaten too much, do you eat less than usual the next day?	☐	☐	☐	☐	☐
17. Do you have a desire to eat when you are cross?	☐	☐	☐	☐	☐

	Never	Rarely	Some times	Often	Almost Always
18. If you walk past a coffee shop or café, do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
19. Do you deliberately eat less in order not to become heavier?	☐	☐	☐	☐	☐
20. Do you have a desire to eat when something unpleasant is about to happen?	☐	☐	☐	☐	☐
21. If you see others eating, do you also have the desire to eat?	☐	☐	☐	☐	☐
22. How often do you try not to eat between meals because you are watching your weight?	☐	☐	☐	☐	☐
23. Do you get the desire to eat when you are anxious, worried or tense?	☐	☐	☐	☐	☐
24. Do you get the desire to eat when things are going against you or have gone wrong?	☐	☐	☐	☐	☐
25. Can you resist eating delicious foods?	☐	☐	☐	☐	☐
26. How often in the evenings do you try not to eat because you are watching your weight?	☐	☐	☐	☐	☐
27. Do you have a desire to eat when you are frightened?	☐	☐	☐	☐	☐
28. Do you take your weight into account with what you eat?	☐	☐	☐	☐	☐

	Never	Rarely	Some times	Often	Almost Always
29. Do you have a desire to eat when you are disappointed?	☐	☐	☐	☐	☐
30. Do you eat more than usual, when you see others eating?	☐	☐	☐	☐	☐
31. Do you have a desire to eat when you are emotionally upset?	☐	☐	☐	☐	☐
32. When preparing a meal are you inclined to eat something?	☐	☐	☐	☐	☐
33. Do you have a desire to eat when you are bored or restless?	☐	☐	☐	☐	☐

Thank you for completing this Questionnaire

Appendix F – B-AHEAD 2 Follow-up Eating and Exercise Questionnaire

Questionnaire:

Eating and Exercise Patterns

1. My views about weight control during treatment

We are interested in what you think about a number of aspects of your weight. Please indicate what you think about your weight by ticking one of the statements below:

☐ I do not think that my current weight is a problem for my health

☐ I think that my current weight is a problem for my health.

Many women with breast cancer gain weight during treatment. We are interested in what you think about weight gain. Please read the statements below and make a mark to indicate how much you agree with each statement. Please answer all questions.

1. My weight gain during treatment was mainly be because of my diet and exercise behaviors.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

☐ Not applicable, I did not gain weight

2. I believe controlling my weight during treatment will reduce the chances of my breast cancer re-occurring.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

3. I have been able to maintain my weight during treatment.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

4. I gained weight during treatment whatever I did.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

☐ Not applicable, I did not gain weight

5. Controlling my weight during treatment was largely dependent upon myself.

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

6. My ability to control my weight during treatment was limited by my treatments and medications

☐ Strongly Agree ☐ Agree ☐ Neither agree or disagree ☐ Disagree ☐Strongly Disagree

2. **Habits**

Please read the statements below and circle a number to indicate how much you agree with each statement. Please answer all questions.

Watching my diet is something…

	Strongly Disagree	Mostly Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Mostly Agree	Strongly Agree
1. I do automatically	1	2	3	4	5	6	7
2. I do without having to consciously remember	1	2	3	4	5	6	7
3. I do without thinking	1	2	3	4	5	6	7
4. I start doing before I realise I'm doing it	1	2	3	4	5	6	7

Exercising regularly is something…

	Strongly Disagree	Mostly Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Mostly Agree	Strongly Agree
1. I do automatically	1	2	3	4	5	6	7
2. I do without having to consciously remember	1	2	3	4	5	6	7
3. I do without thinking	1	2	3	4	5	6	7
4. I start doing before I realise I'm doing it	1	2	3	4	5	6	7

3. How confident are you that you can resist over eating or eating unhealthily in the following situations

Please read the statements below and circle a number to indicate your answer. Please answer all questions.

	Not at all confident	Slightly confident	Quite confident	Very confident	Extremely confident
20) I can resist over eating or eating unhealthily when I am anxious (nervous)	1	2	3	4	5
21) I can resist over eating or eating unhealthily when I am depressed (or down)	1	2	3	4	5
22) I can resist over eating or eating unhealthily when I am angry (or irritable)	1	2	3	4	5
23) I can resist over eating or eating unhealthily when I have experienced failure	1	2	3	4	5
24) I can resist over eating or eating unhealthily when I am bored	1	2	3	4	5
25) I can resist over eating or eating unhealthily when I am thinking negatively about my	1	2	3	4	5
26) I can resist over eating or eating unhealthily when I am worrying about my future health.	1	2	3	4	5
27) I can control my over eating or eating unhealthily on the weekends	1	2	3	4	5
28) I can resist over eating or eating unhealthily when there are many different kinds of food	1	2	3	4	5
29) I can resist over eating or eating unhealthily even when I am eating out or at a party	1	2	3	4	5
30) I can resist over eating or eating unhealthily even when high-calorie foods are available	1	2	3	4	5

31) I can resist over eating or eating unhealthily even when I have to say 'no' to others	1	2	3	4	5
32) I can resist over eating or eating unhealthily even when I feel it's impolite to refuse a	1	2	3	4	5
33) I can resist over eating or eating unhealthily even when others are pressuring me to eat.	1	2	3	4	5
34) I can resist over eating or eating unhealthily even when I think others will be upset if I	1	2	3	4	5
35) I can resist over eating or eating unhealthily when I feel physically run down	1	2	3	4	5
36) I can resist over eating or eating unhealthily when I am in pain	1	2	3	4	5
37) I can resist over eating or eating unhealthily when I feel uncomfortable	1	2	3	4	5

Are you still having regular menstrual cycles? If yes please answer question 19. If no please go to question 20

	Not at all confident	Slightly confident	Quite confident	Very confident	Extremely confident
38) I can resist over eating or eating unhealthily in the week before a period	1	2	3	4	5
20) I can resist over eating or eating unhealthily in the week before my chemotherapy	1	2	3	4	5
21) I can resist over eating or eating unhealthily in the week after my chemotherapy	1	2	3	4	5
22) I can resist over eating or eating unhealthy carbohydrate foods (such as bread, pasta, sweet foods,	1	2	3	4	5

23) I can resist over eating or eating unhealthy carbohydrate foods in the week after my chemotherapy	1	2	3	4	5
24) I can resist over eating or eating unhealthily when I have disrupted sleep patterns	1	2	3	4	5
25) I can resist over eating or eating unhealthily when I am tired	1	2	3	4	5
26) I can resist over eating or eating unhealthily when I feel nauseous	1	2	3	4	5
27) I can resist over eating or eating unhealthily when my sense of taste is altered					
28) I can resist over eating or eating unhealthily when I don't have time to think about my diet	1	2	3	4	5
29) I can resist over eating or eating unhealthily when I have nothing to do	1	2	3	4	5
30) I can resist over eating or eating unhealthily when I am outside my normal routine	1	2	3	4	5
31) I can resist over eating or eating unhealthily when I am watching TV	1	2	3	4	5
32) I can resist over eating or eating unhealthily when I am reading	1	2	3	4	5
33) I can resist over eating or eating unhealthily just before going to bed	1	2	3	4	5
34) I can resist over eating or eating unhealthily when I am happy	1	2	3	4	5

4. My eating style

This section asks about your eating style. Please read the statements below and make a mark to indicate how much you agree with each statement. Please answer all questions.

	Never	**Rarely**	**Some times**	**Often**	**Almost Always**
1. When you have put on weight do you eat less than you usually do?	☐	☐	☐	☐	☐
2. Do you have a desire to eat when you are irritated?	☐	☐	☐	☐	☐
3. If food tastes good to you, do you eat more than usual?	☐	☐	☐	☐	☐
4. Do you try to eat less at mealtimes than you would like to eat?	☐	☐	☐	☐	☐
5. Do you have a desire to eat when you have nothing to do?	☐	☐	☐	☐	☐
6. If food smells and looks good, do you eat more than usual?	☐	☐	☐	☐	☐
7. How often do you refuse food or drink offered because you are concerned about your weight?	☐	☐	☐	☐	☐
8. Do you have a desire to eat when you are depressed or discouraged?	☐	☐	☐	☐	☐

	Never	Rarely	Some times	Often	Almost Always
9. If you see or smell something delicious, do you have a desire to eat it?	☐	☐	☐	☐	☐
10. Do you watch exactly what you eat?	☐	☐	☐	☐	☐
11. Do you have a desire to eat when you are feeling lonely?	☐	☐	☐	☐	☐
12. If you have something delicious to eat, do you eat it straight away?	☐	☐	☐	☐	☐
13. Do you deliberately eat foods that are slimming?	☐	☐	☐	☐	☐
14. Do you have a desire to eat when somebody lets you down?	☐	☐	☐	☐	☐
15. If you walk past the baker do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
16. When you have eaten too much, do you eat less than usual the next day?	☐	☐	☐	☐	☐
17. Do you have a desire to eat when you are cross?	☐	☐	☐	☐	☐
18. If you walk past a coffee shop or café, do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
19. Do you deliberately eat less in order not to become heavier?	☐	☐	☐	☐	☐
20. Do you have a desire to eat when something unpleasant is about to happen?	☐	☐	☐	☐	☐

	Never	Rarely	Some times	Often	Almost Always
21. If you see others eating, do you also have the desire to eat?	☐	☐	☐	☐	☐
22. How often do you try not to eat between meals because you are watching your weight?	☐	☐	☐	☐	☐
23. Do you get the desire to eat when you are anxious, worried or tense?	☐	☐	☐	☐	☐
24. Do you get the desire to eat when things are going against you or have gone wrong?	☐	☐	☐	☐	☐
25. Can you resist eating delicious foods?	☐	☐	☐	☐	☐
26. How often in the evenings do you try not to eat because you are watching your weight?	☐	☐	☐	☐	☐
27. Do you have a desire to eat when you are frightened?	☐	☐	☐	☐	☐
28. Do you take your weight into account with what you eat?	☐	☐	☐	☐	☐
29. Do you have a desire to eat when you are disappointed?	☐	☐	☐	☐	☐
30. Do you eat more than usual, when you see others eating?	☐	☐	☐	☐	☐
31. Do you have a desire to eat when you are emotionally upset?	☐	☐	☐	☐	☐

	Never	Rarely	Some times	Often	Almost Always
32. When preparing a meal are you inclined to eat something?	☐	☐	☐	☐	☐
33. Do you have a desire to eat when you are bored or restless?	☐	☐	☐	☐	☐

5. Satisfaction with the Interventions

Please read the statements below and circle a number to indicate your answer. Please answer all questions.

1) "Given the effort you have put into watching your diet how satisfied are you with your progress?"

Very Dissatisfied				Neither Satisfied nor Dissatisfied				Very Satisfied
-4	-3	-2	-1	0	1	2	3	4

2) "How satisfied are you with what you have experienced as a result of watching your diet?"

Very Dissatisfied				Neither Satisfied nor Dissatisfied				Very Satisfied
-4	-3	-2	-1	0	1	2	3	4

3) "Given the effort you have put into doing exercise, how satisfied are you with your progress?"

Very Dissatisfied				Neither Satisfied nor Dissatisfied				Very Satisfied
-4	-3	-2	-1	0	1	2	3	4

4) "How satisfied are you with what you have experienced as a result of doing exercise?"

Very Dissatisfied				Neither Satisfied nor Dissatisfied				Very Satisfied

-4 -3 -2 -1 0 1 2 3 4

Thank you for completing this Questionnaire

Appendix G – B-AHEAD 2 Interview 1 Topic guide (end of treatment)

Recruitment/Baseline appt

- What do they think of the timing of recruitment?
- Overburdened at this time/decisional balance?
- Is it appropriate to raise diet and exercise at this time?
    - Does this raise feelings of guilt attributions to diagnosis?

What motivated them to join?

- How important did they feel losing weight / maintaining weight was at the start of the study? Had this changed by the end of the study?
- Interesting to talk to women who did not join

Compliance with diet and exercise

- Difficulties of following 2 day or daily diet at different times of chemo cycle
- Disappointed not on test diet

What was their main focus diet or exercise

- What prevented them from sticking to their targets during chemo? / if you met your targets, what motivated you to do this during such a difficult time and how do you think you managed it?
- How did they feel if they could not comply? guilt
- Patient burden: did we stress them out with our targets or did they like having something else to really focus on?
- Did they have many friends and family contradicting the advice/targets we had set for them?

- Did their opinions alter because of this? How did they cope with this? Or buy in support
- Same question above but for contradictions from health professionals they met along their treatment journey – or buy in support

Support

- Initial advice session face to face
- Summary is time consuming for us to produce…helpful? Any suggested changes?
- Phone calls: helpful?
- ? trusted source and appreciate our expertise . Could anyone else ring?
- Our knowledge: did they feel that we understood the treatments that they were going through and was it important to them that we had this knowledge?
- Did they view the study as an integral part of their treatment or was it distinctively separate?
- Did they want face to face / Web support / Peer group support

Need for information

- Healthy tips sheets: did they read them? Helpful? Any suggested changes?
- ? Required other info

Moving forward

- Will they keep to diet after study
- Do you package diet and exercise and treatment and not want to continue (develop barriers)
- Evaluating study process

- Views about baseline appointment and any changes they would suggest? Was the baseline appointment letter adequate enough to give them a good idea of what they would be doing on the day?
- Are they glad they joined the study? Why?!
- Do they think other pts should be offered this type of support
- Do you want peer support or not a packaged during treatment

Appendix H – B-AHEAD 2 Interview 2 Topic Guide (6 months post end of treatment)

Questions	
Identity – sense of agency	
Since finishing the BAHEAD study have you carried on with diet/exercise advice?	
Have you changed your diet plan? Why?	
What have been your motivations to lose weight? Are they the same motivations as before?	Cancer prevention? Aesthetics? Control over risk? Physical feedback from diet? Health as anchor point.
How long do you plan to carry on following diet for?	
Has this been different without the support of a dietitian?	
Anchor points	
Has this become more of a lifestyle for you? Is it a return to how you ate before having cancer?	Anchor point as a constituent of their identity as healthy people
	Religion, family, social networks, travel, work, approval of others, health, privacy
Incorporation & reconstruction	

Have family members or friends begun following diet/lifestyle advice?	Incorporation of cancer experience to benefit others
Do you see healthy diet and lifestyle as impacting on the risk of developing cancer/cancer recurrence?	
Has having cancer motivated you to stick to diet plan?	Incorporation of cancer experience into new ways to lose weight.
Have you stuck rigidly to the plan set out in the BAHEAD study or have you changed anything?	Reconstructing old diet experiences into current weight loss attempts.
Imbuing experience with meaning	
Has being part of the BAHEAD study and trying to follow diet and lifestyle advice during chemotherapy influenced how you think about diet and lifestyle?	